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Reactions of 5,8-dichloro-2,3-dicyanoquinoxaline with amines and hydrazines. A new and efficient synthetic approach to 3-amino-5,8-dichloroflavazoles

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ABSTRACT

Reactions of 5,8-dichloro-2,3-dicyanoquinoxaline with primary amines and hydrazines under different experimental conditions were investigated. Alkylamines provided novel 3-alkylamino-5,8-dichloro-2-cyanoquinoxalines and *N*-alkyl-(5,8-dichloro-3-alkylamino-2-quinoxalinyl)carboxamidines in high yields. Alkylhydrazines and lithium arylhydrazinides gave previously unattainable 1-alkyl-3-amino-5,8-dichloroflavazoles and 3-amino-1-aryl-5,8-dichloroflavazoles in good to near quantitative yields whose molecular structure was confirmed by X-ray crystallography of 3-[*N*,*N*-bis(4-chlorobenzoyl) amino]-5,8-dichloro-1-phenylflavazole. Reaction with hydrazine gave 5,8-dichloro-3-hydrazino-2-quinoxalinylcarboxamidrazone quantitatively, which was converted to the parent compound of this class of flavazoles, 3-amino-5,8-dichloroflavazole, in high yield by a pyrolytic process involving loss of hydrazine.
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1. Introduction

Over the last years the chemistry of flavazoles has received much attention mainly due to the pharmacological properties.[1–11] These substances have also been reported useful as dyes,[12–15] as photoinitiators for free radical polymerization reactions,[16] and as UV filters in the manufacture of skin lotions.[17] Particularly, 3-aminoflavazole is currently under intense investigation as a specific inhibitor of certain proteins.[3,4,18]

The preferred methodology for preparing 3-aminoflavazoles uses 3-chloro-2-cyanoquinoxaline as starting material,[3,18–21] which is obtainable from benzofuroxane,[22–28] or from 2-carboxamido-3-hydroxyquinoxaline.[20,29] Other methodologies involve intermediates with the previously formed flavazole ring system. These compounds are subjected to C(3)-chlorination and subsequent amination,[30] Hofmann degradation (of 3-carboxamidoflavazoles)[30] or Curtius rearrangement (of 3-hydrazinocarbonylflavazoles).[31–35] It should be pointed out that the need for 3-aminoflavazoles functionalized at the benzene ring has been underlined in order to establish a good relationship between structure and biological activity of these substances.[3] In view of this, and regarding our methodology for the synthesis of selectively chlorinated heterocyclic compounds throughout polychloro-cyclohexanediones,[36–40] which demonstrated to be excellent synthetic equivalents of unavailable chlorinated *o*-benzoquinones, we recognised the opportunity to investigate a plausible approach to unprecedented 3-amino-5,8-dichloroflavazoles, whose synthesis appears to be unfeasible by previously established preparative methods. Thus, 2-cyano-3,5,8-trichloroquinoxaline could be considered as a good intermediate for the synthesis of compounds **7**,**8**,**10**. However, it is an unknown substance whose preparation would involve either 3,6-dichloro-1,2-phenylenediamine or 4,7-dichlorobenzofuroxane. Nevertheless, these are rare, expensive and unavailable intermediates in practice. The most efficient preparations yielded only 15%[36,41] and 10%,[42,43] respectively. On the other hand, chlorination at C(5) and C(8) of the flavazole rings system seems unfeasible since the only chlorination products reported for flavazoles are 3-chloroflavazole[1] and 1-(*p*-chlorophenyl)flavazole.[44]

Recently, we developed a new and efficient synthetic approach to 7,10-dichlorofluoflavines.[36] This paper reported the first synthesis of 5,8-dichloro-2,3-dicyanoquinoxaline **3**, which was used as a key intermediate able to act as a synthetic equivalent of unavailable 2,3,5,8-tetrachloroquinoxaline. Quinoxaline **3** reacted with substituted 1,2-diaminobenzenes providing the targeted new fluoflavine products in fair to high yields. Compound **3** was easily obtained in quantitative yield[36] from 3,3,6,6-tetrachloro-1,2-cyclohexanodione **1** (Scheme 1), a cheap and readily available intermediate,[40] which we used in developing efficient synthetic methods for different families of chlorinated phenazines[37–40] as well as specifically chlorinated 1,2-epoxycyclopentane-1-carboxylic acids and their alkyl esters.[45] Given that **1** can be used as a synthetic equivalent of unavailable 3,6-dichloro-1,2-benzoquinone, we successfully attempted to react it with diaminomaleonitrile **2** to provide product **3** in quantitative yield (Scheme 1).

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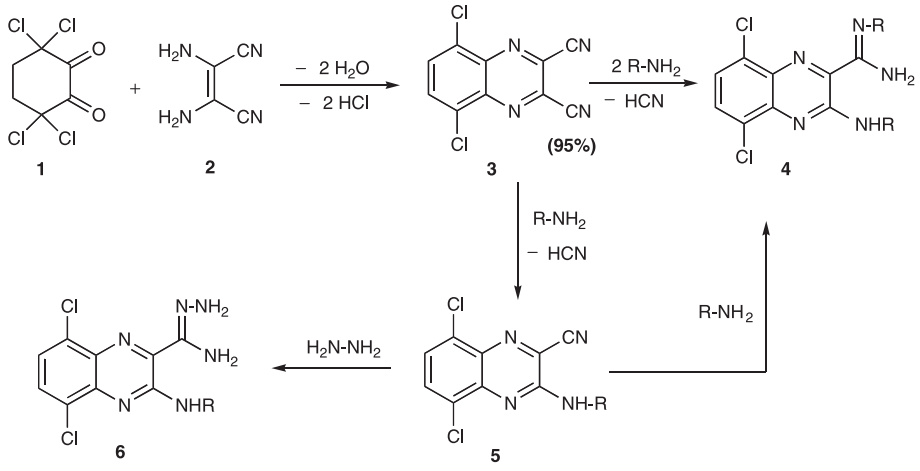


Entry	R	Yield (%)
4a	Me	95
4b	Pr	92
5a	H	95
5b	Me	92
5c	Pr	90
6a	H	89
6b	Me	91
6c	Pr	95

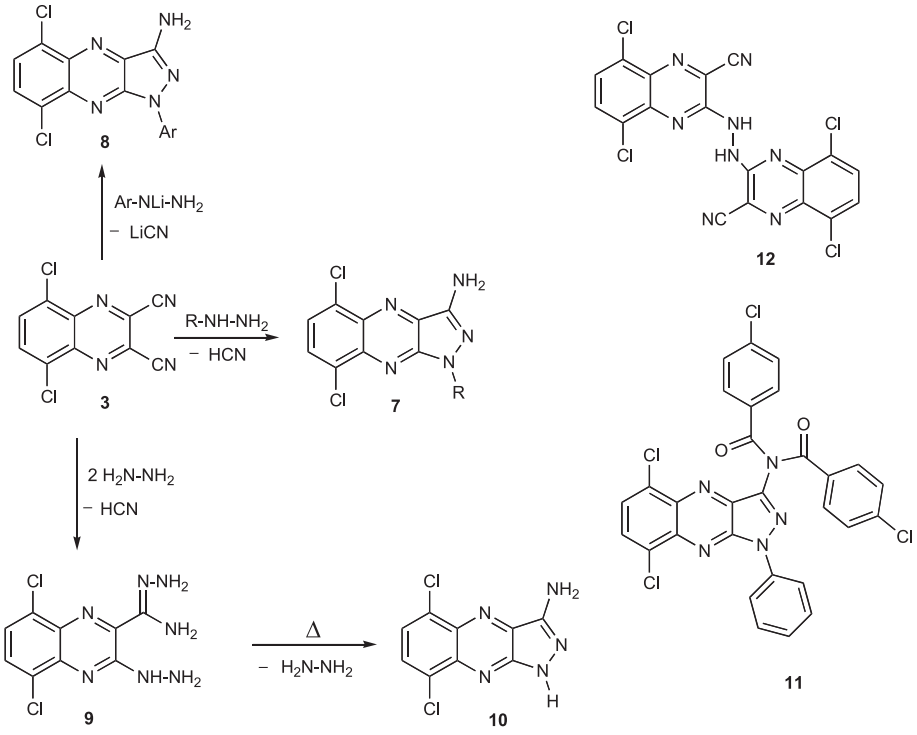
Scheme 1.

On exploring reactions between nucleophilic reagents and 5,8-dichloro-2,3-dicyanoquinoxaline **3** we found a crucially different chemical behaviour in this compound from that of its non-chlorinated analogous, 2,3-dicyanoquinoxaline. For example, 2,3-dicyanoquinoxaline reacts with ammonia[46] or hydrazine[47–49] undergoing nucleophilic addition to cyano groups, whereas **3** gives products involving nucleophilic aromatic substitution of a cyano group. It seems clear that the opposite behaviour between these compounds would be caused by the conjunction of electro-withdrawing groups present in **3**. Related reactions in quinoxaline derivatives have been described for 2,3-dichloroquinoxaline[47,50] and 3-chloro-2-cyanoquinoxaline,[19,25] where nucleophilic displacement of the chlorine atom occurs, but not for a cyano group. These facts strongly suggested the opportunity to expand the range of synthetic applications of our preparative methodology to achieve the synthesis of the title flavazole compounds.

2. Results and discussion

Room temperature treatment of 5,8-dichloro-2,3-dicyanoquinoxaline **3** with methylamine or propylamine in excess, in the presence of triethylamine, gave single products that were isolated and identified as *N*-alkyl-(3-alkylamino-5,8-dichloro-2-quinoxalinyl)carboxamidines **4** (Scheme 1). Yields were near to quantitative. Obviously, the formation of these products implies two different nucleophilic attack processes by part of alkylamine molecules: addition to cyano group and cyano group substitution. Considering that the electronic effect of an amino group attached to an aromatic nucleus causes a drastic lowering on electrophilic activity, the observed disparity in behaviour between both cyano groups of **3** is explainable as result of a reaction sequence involving a first substitution process followed by a second addition step, rather than a reaction occurring in the inverse order (first addition followed by substitution). In this manner, a first substitution attack would prevent a second substitution process, leaving only the alternative of addition. This was evidenced by experiments carried out by lowering the amount of amine until a 1:1 ratio. Under these conditions the formed products were 3-amino-5,8-dichloro-2-cyanoquinoxalines **5**, which were isolated in high yield and whose formation corresponds to selective substitution in complete absence of competitive addition (Scheme 1). The reaction with ammonia was similar. Moreover, the ability of compounds **5** to undergo addition to the stationary cyano group was corroborated by treatment with methylamine, propylamine and hydrazine at rt, since these reactions provided the corresponding carboxamidines **4** and carboxamidrazones **6**, respectively, in near quantitative yields. The synthesis of compounds **4**,**5**,**6** has not been previously reported.

Taking into consideration that dinucleophilic reagents could operate accordingly to experiments described above, promoting first substitution followed by intramolecular addition, we envisaged an attractive possibility of development of a good new preparative method for previously unattainable 3-amino-5,8-dichloroflavazoles by direct reaction of intermediate **3** with hydrazines, as shown in Scheme 2. Working on this idea the reaction of **3** with alkylhydrazines at rt gave successful results. As expected, direct formation of 1-alkyl-3-amino-5,8-dichloroflavazoles **7**, in near quantitative yields, was observed. However, a similar treatment of **3** with hydrazine (ratio 1:1) gave a disappointing result, leading to a complex mixture of reaction products. The main component of this mixture gave a mass spectrum proving to be a dimeric compound **12** instead of 3-amino-5,8-dichloroflavazole **10**. It should be noted that formation of **12** would proceed from a cyanoquinoxalinyl hydrazine intermediate, which would attack starting material molecules **3**. Such an intermolecular reaction would be faster than the alternative internal addition process to the vicinal cyano group leading to the corresponding flavazole **10**. This is a contrary behaviour to that observed with alkylhydrazines. Nevertheless, it can be reasonably explained in view of the expected electron withdrawing effect of a quinoxalinyl group lowering the nucleophilic activity of hydrazine, but being compensated by the presence of *N*-alkyl substituents. The



Entry		Yield (%)
7a	R= CH_3	98
7b	R= CH_3CH_2	96
7c	R= $HOCH_2CH_2$	92
8a	Ar= C_6H_5	67
8b	Ar= 4-$MeOC_6H_4$	78
8c	Ar= 4-t-BuC_6H_4	63
9		96
10		83
11		95

Scheme 2.

result of a similar reaction, but increasing the hydrazine amount (ratio 1:2), quantitatively yielding 5,8-dichloro-3-hydrazino-2-quinoxalinylcarboxamidrazone **9** provided support to this hypothesis. In spite of this fact, the targeted parent compound of this family of flavazoles could be achieved by pyrolysis of **9**, since when it was heated up to 200 °C it gave 3-amino-5,8-dichloroflavazole **10** in high yield by loss of hydrazine.

Continuing the work in this project, we attempted unsuccessfully the synthesis of 3-amino-1-aryl-5,8-dichloroflavazoles **8** by direct reaction of intermediate **3** with arylhydrazines. It was presumed that this failed result could be due to a relatively weaker nucleophilic activity of arylhydrazines than alkylhydrazines. This assumption was confirmed by testing the synthesis with lithium arylhydrazinides generated by treatment arylhydrazines with LDA. In this case the corresponding flavazoles **8** were obtained in moderate to high yields. Unfortunately, single crystals suitable for an X-ray diffraction analysis of one of the prepared flavazoles could not be obtained despite intensive effort. Instead, we were successful in an attempt to analyze a dibenzoylated derivative. The molecular structure determined corresponds to 3-[*N*,*N*-bis(4-chlorobenzoyl) amino]-5,8-dichloro-1-phenylflavazole **11**, (Fig. 1). Selected intramolecular distances and bond angles for this crystal structure are given in Table 1. Fig. 2 corresponds to a perspective of the crystal packing, showing hydrogen interactions of molecules with a double chain arrangement.

In conclusion, a proficient and general new method for the synthesis of 3-amino-5,8-dichloroflavazoles on the basis of 5,8-dichloro-2,3-dicyanoquinoxaline chemistry is reported. Good yields and easy availability of starting materials are valuable, noteworthy advantages of the method, which allows a privileged access to previously unattainable products. The high interest of 5,8-dichloro-2,3-dicyanoquinoxaline as synthetic intermediate for a wide range of quinoxaline derivatives has also been demonstrated. Not only are the prepared compounds of interest in themselves, but also their chlorine substituents suggest an attractive synthetic potential to be explored.

3. Experimental

3.1. General

NMR spectra were determined on Bruker AV-200, Bruker AV-300 or Bruker AV-400 with tetramethylsilane as internal reference. Electron-impact mass spectra were obtained on Thermoquest trace MS spectrometer under an ionizing voltage of 70 eV. IR spectra (Nujol emulsions) were recorded on a Nicolet Impact 400 Spectrometer. Microanalyses were performed on a Carlo Erba EA-1108 analyzer. Melting points were determined on a Büchi Melting point B-540, and are uncorrected. Compounds **1** and **3** were prepared as previously described.[36,40]

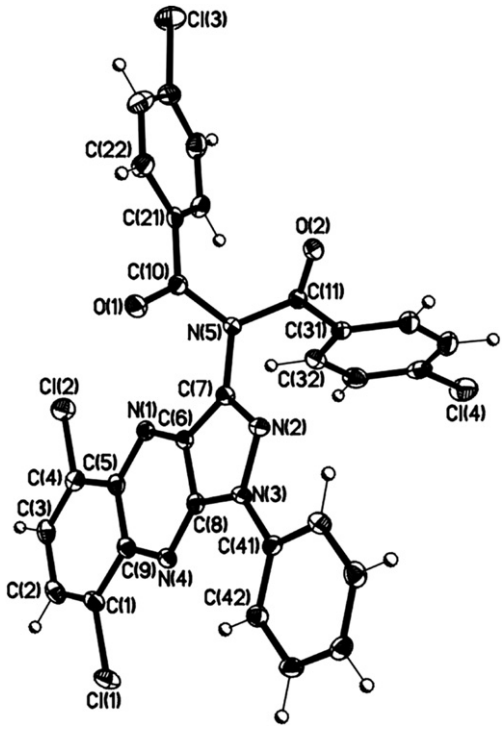


Fig. 1. Thermal ellipsoid plot (50% level) of compound **11** in the crystal.

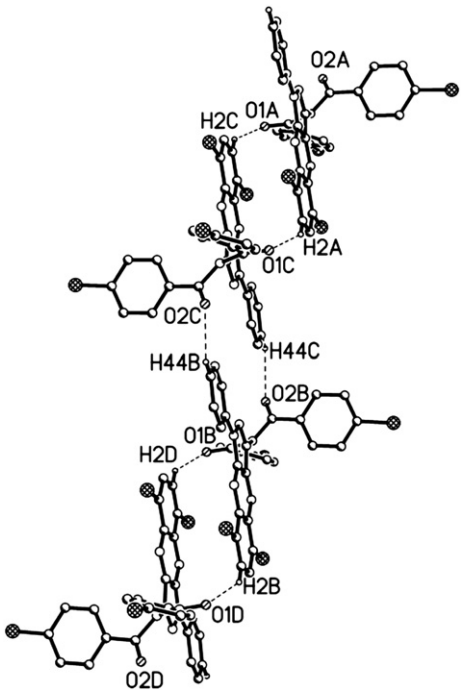


Fig. 2. A perspective of the crystal packing of **11**, showing the hydrogen interactions of molecules with a double chain arrangement.

Table 1
Selected bond lengths and bond angles in crystal structure of **11**

Bond lengths (Å)			
Cl(1)–C(1)	1.730(2)	N(4)–C(8)	1.314(3)
C(1)–C(2)	1.359(3)	C(6)–C(7)	1.426(3)
C(2)–C(3)	1.409(3)	N(2)–C(7)	1.310(3)
C(4)–C(5)	1.430(3)	N(2)–N(3)	1.378(2)
N(1)–C(5)	1.355(3)	N(5)–C(7)	1.413(3)
N(1)–C(6)	1.323(3)	N(5)–C(10)	1.430(3)
Bond angles (°)			
N(2)–C(7)–C(6)	111.46(18)	N(2)–N(3)–C(41)	119.84(16)
C(7)–N(5)–C(10)	116.30(16)	N(3)–C(8)–C(6)	106.83(17)
C(7)–N(5)–C(11)	118.06(16)	C(8)–N(3)–C(41)	130.02(17)
C(11)–N(5)–C(10)	119.32(16)	N(5)–C(10)–C(21)	115.83(17)
C(7)–N(2)–N(3)	107.41(17)	N(5)–C(7)–C(6)	127.97(19)
C(8)–N(3)–N(2)	110.14(16)	N(2)–C(7)–N(5)	120.55(18)

3.2. Preparation of *N*-alkyl-(3-alkylamino-5,8-dichloro-2-quinoxalinyl)carboxamidines 4

To a solution of **3** (2 mmol) in THF (10 ml) a solution of the corresponding amine (6 mmol) and triethylamine (2.2 mmol) in THF (5 ml) was added dropwise. The mixture was stirred at rt for 3 h. Then the solvent was concentrated to dryness under reduced pressure and the solid obtained was washed with water, collected by filtration and crystallized from the appropriate solvent.

*3.2.1. N-Methyl-(5,8-dichloro-3-methylamino-2-quinoxalinyl)carboxamidine (**4a**).* Yield: 95%; crystallization from ethanol gave yellow needles; mp 155–156 °C. (Found C 46.64; H 3.84; N 24.57; $C_{11}H_{11}Cl_2N_5$ requires C 46.50; H 3.90; N 24.65); ^{1}H NMR δ ($CDCl_3$, 400 MHz) 3.03 (s, 3H, NCH_3)*, 3.04 (s, 3H, $NHCH_3$)*, 6.76 (br s, 2H, NH_2), 7.42 (d, 1H, J=8.3 Hz, H-7), 7.69 (d, 1H, J=8.3 Hz, H-6), 10.81 (br s, 1H, NH); ^{13}C NMR δ ($CDCl_3$, 100.8 MHz) 27.12 (CH_3), 35.56 (CH_3), 122.82 (CH), 126.82 (C), 130.14 (CH), 130.56 (C), 130.61 (C), 134.11 (C), 140.07 (C), 152.19 (C), 155.73 (C); MS m/z (%) 285 (M^++2, 64), 283 (M^+, 100), 268 (21), 255 (21), 253 (35), 238 (47), 198 (25), 171 (12), 149 (13), 88 (10), 57 (51); IR (Nujol) 3500, 3381, 1641, 1567, 1535, 1229, 1192, 1167, 1133, 1109, 1052, 968, 935, 815, 794, 663 cm^{-1}.

*3.2.2. N-Propyl-(5,8-dichloro-3-propylamino-2-quinoxalinyl)carboxamidine (**4b**).* Yield: 92%; crystallization from methanol gave yellow needles; mp 80–81 °C. (Found C 53.07; H 5.57; N 20.65; $C_{15}H_{19}Cl_2N_5$ requires C 52.95; H 5.63; N 20.58); ^{1}H NMR δ ($CDCl_3$, 300 MHz) 1.02–1.09 (m, 6H, CH_3), 1.69–1.82 (m, 4H, CH_2CH_3), 3.18 (t, 2H, J=6.8 Hz, NCH_2Et), 3.60 (q, 2H, J=6.6 Hz, $NHCH_2Et$), 5.82 (br s, 2H, NH_2), 7.25 (d, 1H, J=8.2 Hz, H-7), 7.54 (d, 1H, J=8.2 Hz, H-6), 10.78 (br s, 1H, NH); ^{13}C NMR δ ($CDCl_3$, 75.4 MHz) 11.84 (CH_3), 12.01 (CH_3), 22.07 (CH_2), 23.71 (CH_2), 42.61 (CH_2), 49.90 (CH_2), 122.45 (CH), 127.89 (C), 129.77 (CH), 131.18 (C), 131.39 (C), 133.56 (C), 141.04 (C), 152.09 (C), 154.26 (C); EM, m/z (%) 341 (M^++2, 12), 339 (M^+, 19), 312 (67), 310 (100) 293 (14), 253 (60), 251 (86), 238 (11), 197 (19); IR (Nujol) 3433, 3326, 3165, 3071, 2963, 2924, 2870, 1643, 1569, 1534, 1449, 1377, 1353, 1333, 1289, 1224, 1192, 1102, 976, 934, 809, 765, 703, 669 cm^{-1}.

3.3. Preparation of 3-amino-5,8-dichloro-2-cyanoquinoxalines 5

To an ice-cooled solution of **3** (2 mmol) in THF (10 ml) a solution of the corresponding amine (2 mmol) and triethylamine (2.2 mmol) in THF (5 ml) was added dropwise, keeping the temperature below 0 °C. In the case of compound **5a** a 5% solution of ammonia–THF was used and the temperature was raised to rt. The mixture was stirred until the consumption of **3** (detected by TLC). Then the solvent was concentrated to dryness under reduced pressure and the solid obtained was washed with water, collected by filtration and crystallized from the appropriate solvent.

*3.3.1. 3-Amino-5,8-dichloro-2-cyanoquinoxaline (**5a**).* Yield: 95%; crystallization from acetonitrile gave yellow plates; mp >320 °C. (dec). (Found C 45.36; H 1.72; N 23.36; $C_9H_4Cl_2N_4$ requires C 45.22; H 1.69; N 23.44); ^{1}H NMR δ (DMSO-d_6, 400 MHz) 7.54 (d, 1H, J=8.2 Hz, H-7), 7.83 (d, 1H, J=8.2 Hz, H-6), 7.95 (br s, 2H, NH_2); ^{13}C

NMR δ (DMSO-d_6, 100.8 MHz) 114.69 (C), 120.85 (C), 124.60 (CH), 127.43 (C), 131.15 (C), 132.54 (CH), 132.82 (C), 140.58 (C), 153.30 (C); EM, *m*/*z* (%) 240 (M^++2, 67), 238 (M^+, 100), 213 (27), 211 (40), 188 (21), 186 (31), 158 (24), 151 (32), 144 (27), 124 (22), 109 (31), 88 (27); IR (Nujol) 3407, 3323, 3242, 3215, 2239, 1643, 1557, 1430, 1355, 1225, 1206, 1105, 1154, 957, 944, 836, 665 cm^{-1}.

*3.3.2. 5,8-Dichloro-2-cyano-3-methylaminoquinoxaline (**5b**).* Yield: 92%; crystallization from ethanol gave yellow needles; mp 249–251 °C (Found C 47.54; H 2.45; N 22.23; $C_{10}H_6Cl_2N_4$ requires C 47.46; H 2.39; N 22.14); ^{1}H NMR δ (DMSO-d_6, 400 MHz) 2.98 (d, 3H, *J*=4.3 Hz, CH_3), 7.53 (d, 1H, *J*=8.2 Hz, H-7), 7.84 (d, 1H, *J*=8.2 Hz, H-6), 8.18 (q, 1H, *J*=4.3 Hz, NH); ^{13}C NMR δ (DMSO-d_6, 50.4 MHz) 28.03 (CH_3), 114.54 (C), 121.87 (C), 124.45 (CH), 127.70 (C), 131.12 (C), 132.35 (C), 132.53 (CH), 140.32 (C), 152.02 (C); EM, *m*/*z* (%) 254 (M^++2, 65), 252 (M^+, 100), 227 (8), 225 (13) 198 (31), 171 (12), 158 (13), 144 (7), 109 (8), 88 (9); IR (Nujol) 3392, 2231, 1599, 1574, 1445, 1339, 1227, 1199, 1155, 1105, 967, 951, 827, 797, 698, 665, 607 cm^{-1}.

*3.3.3. 5,8-Dichloro-2-cyano-3-propylaminoquinoxaline (**5c**).* Yield: 90%; crystallization from acetonitrile gave yellow plates; mp 177–179 °C (Found C 51.38; H 3.54; N 19.88; $C_{12}H_{10}Cl_2N_4$ requires C 51.27; H 3.59; N 19.93); ^{1}H NMR δ ($CDCl_3$, 400 MHz) 1.06 (t, 3H, *J*=7.2 Hz, CH_3), 1.79 (sex, 2H, *J*=7.2 Hz, CH_2CH$_3$), 3.65 (q, 2H, *J*=7.2 Hz, CH_2Et), 5.70 (br s, 1H, NH), 7.42 (d, 1H, *J*=8.2 Hz, H-7), 7.68 (d, 1H, *J*=8.2 Hz, H-6); ^{13}C NMR δ ($CDCl_3$, 100.8 MHz) 11.56 (CH_3), 22.10 (CH_2), 43.50 (CH_2), 114.22 (C), 120.74 (C), 125.12 (CH), 129.23 (C), 132.46 (C), 132.55 (CH), 133.72 (C), 140.74 (C), 151.55 (C); EM, *m*/*z* (%) 282 (M^++2, 27), 280 (M^+, 41), 267 (9), 265 (14), 253 (49), 251 (70), 240 (66), 238 (100), 213 (16), 197 (37), 170 (12), 134 (13), 88 (9); IR (Nujol) 3365, 2235, 1598, 1567, 1342, 1225, 1153, 1104, 982, 945, 829, 665 cm^{-1}.

3.4. Preparation of 3-alkylamino-5,8-dichloro-2-quinoxalinylcarboxamidrazones 6

To a solution of the corresponding 3-amino-5,8-dichloro-2-cyanoquinoxaline **5** (2 mmol) in THF (10 ml) an aqueous solution of hydrazine 55% (2 ml) was added dropwise. The mixture was stirred at rt for 4 h. Then the solvent was concentrated to dryness under reduced pressure and the solid obtained was washed with water, collected by filtration and crystallized from the appropriate solvent.

*3.4.1. 3-Amino-5,8-dichloro-2-quinoxalinylcarboxamidrazone (**6a**).* Yield: 89%; crystallization from ethanol gave yellow needles; mp >320 °C (dec) (Found C 39.99; H 2.91; N 30.92; $C_9H_8Cl_2N_6$ requires C 39.87; H 2.97; N 31.00); ^{1}H NMR δ (DMSO-d_6, 300 MHz) 5.98 (br s, 2H, NH_2), 6.13 (br s, 2H, NH_2), 7.45 (d, 1H, *J*=8.3 Hz, H-7), 7.66 (d, 1H, *J*=8.3 Hz, H-6), 7.99 (br s, 1H, NH), 9.15 (br s, 1H, NH); ^{13}C NMR δ (DMSO-d_6, 75.4 MHz) 123.06 (CH), 126.39 (C), 128.99 (CH), 130.07 (C), 131.77 (C), 134.26 (C), 138.74 (C), 143.50 (C), 151.76 (C); EM, *m*/*z* (%) 272 (M^++2, 69), 270 (M^+, 100), 241 (49), 214 (30), 186 (19), 158 (11), 149 (14), 124 (7), 88 (7); IR (Nujol) 3428, 3303, 1651, 1605, 1577, 1239, 1131, 1108, 954, 909, 807, 743, 667 cm^{-1}.

*3.4.2. 5,8-Dichloro-3-methylamino-2-quinoxalinylcarboxamidrazone (**6b**).* Yield: 91%; crystallization from methanol gave yellow needles; mp 210–220 °C (dec) (Found C 42.20; H 3.58; N 29.53; $C_{10}H_{10}Cl_2N_6$ requires C 42.12; H 3.53; N 29.47); ^{1}H NMR δ (DMSO-d_6, 400 MHz) 3.07 (d, 3H, *J*=4.8 Hz, CH_3), 5.99 (br s, 2H, NH_2), 6.10 (br s, 2H, NH_2), 7.41 (d, 1H, *J*=8.3 Hz, H-7), 7.64 (d, 1H, *J*=8.3 Hz, H-6), 9.73 (q, 1H, *J*=4.8 Hz, NH); ^{13}C NMR δ (DMSO-d_6, 100.8 MHz) 27.36 (CH_3), 122.84 (CH), 126.73 (C), 128.96 (CH), 130.01 (C), 131.16 (C), 134.44 (C), 138.67 (C), 143.62 (C), 150.96 (C); EM, *m*/*z* (%) 286 (M^++2, 35), 284 (M^+, 51), 270 (60), 268 (100), 253 (44), 239 (16), 199 (18), 171 (15), 149 (14), 127 (10), 109 (9), 100 (8); IR (Nujol) 3465, 3355, 1633, 1606, 1579, 1538, 1397, 1233, 1191, 1129, 1108, 968, 945, 840, 795, 665 cm^{-1}.

*3.4.3. 5,8-Dichloro-3-propylamino-2-quinoxalinylcarboxamidrazone (**6c**).* Yield: 95%; crystallization from methanol–water gave yellow needles; mp 130–132 °C. (Found C 45.91; H 4.58; N 26.79; $C_{12}H_{14}Cl_2N_6$ requires C 46.02; H 4.51; N 26.83); ^{1}H NMR δ (DMSO-d_6, 400 MHz) 0.96 (t, 3H, *J*=7.3 Hz, CH_3), 1.67 (sex, 2H, *J*=7.3 Hz, CH_2CH$_3$), 3.49–3.54 (m, 2H, CH_2Et), 6.00 (br s, 2H, NH_2), 6.14 (br s, 2H, NH_2), 7.39 (d, 1H, *J*=8.2 Hz, H-7), 7.63 (d, 1H, *J*=8.2 Hz, H-6), 9.87 (t, 1H, *J*=5.0 Hz, NH); ^{13}C NMR δ (DMSO-d_6, 100.8 MHz) 11.73 (CH_3), 21.63 (CH_2), 42.16 (CH_2), 122.79 (CH), 126.71 (C), 128.92 (CH), 129.99 (C), 131.15 (C), 134.20 (C), 138.66 (C), 143.75 (C), 150.38 (C); EM, *m*/*z* (%) 314 (M^++2, 26), 312 (M^+, 38), 298 (21), 296 (32), 285 (62), 283 (100), 268 (53), 266 (77), 239 (40), 214 (26), 197 (33), 186 (22), 158 (18), 149 (23), 124 (14), 88 (19); IR (Nujol) 3443, 3346, 3246, 1634, 1567, 1531, 1225, 1192, 1132, 1106, 979, 941, 817, 668 cm^{-1}.

3.5. Preparation of 1-alkyl-3-amino-5,8-dichloroflavazoles 7

To a solution of **3** (2 mmol) in THF (10 ml) a solution of the corresponding alkylhydrazine (3 mmol) and triethylamine (2.2 mmol) in THF (5 ml) was added dropwise. The mixture was stirred at rt until the consumption of **3** (detected by TLC). Then the solvent was concentrated to dryness under reduced pressure and the solid obtained was washed with water, collected by filtration and crystallized from the appropriate solvent. In the case of compound **7b** the solvent used was DMF to allow a higher solubility of the commercial oxalate salt of ethylhydrazine used. The isolation of product was carried out by pouring the reaction mixture into cold brine (200 ml), followed by filtration and crystallization of the precipitated solid.

*3.5.1. 3-Amino-5,8-dichloro-1-methylflavazole (**7a**).* Yield: 98%; crystallization from ethanol gave red needles; mp 217–219 °C. (Found C 44.93; H 2.72; N 26.03; $C_{10}H_7Cl_2N_5$ requires C 44.80; H 2.63; N 26.12.); ^{1}H NMR δ (DMSO-d_6, 300 MHz) 3.83 (s, 3H, CH_3), 6.40 (br s, 2H, NH_2), 7.67 (d, 1H, *J*=8.1 Hz, H-6), 7.84 (d, 1H, *J*=8.1 Hz, H-7); ^{13}C NMR δ (DMSO-d_6, 75.4 MHz) 33.16 (CH_3), 125.07 (CH), 129.35 (C), 129.82 (CH), 131.69 (C), 131.98 (C), 134.97 (C), 138.62 (C), 141.59 (C), 147.89 (C); MS *m*/*z* (%) 269 (M^++2, 63), 267 (M^+, 100), 241 (8), 239 (13), 199 (11), 197 (18), 161 (12), 134 (13); IR (Nujol) 3388, 3302, 1631, 1607, 1559, 1204, 1186, 1094, 1050, 986, 938, 836 cm^{-1}.

*3.5.2. 3-Amino-5,8-dichloro-1-ethylflavazole (**7b**).* Yield: 96%; crystallization from acetonitrile gave red needles; mp 174–176 °C. (Found C 46.95; H 3.17; N 24.73; $C_{11}H_9Cl_2N_5$ requires C 46.83; H 3.22; N 24.82); ^{1}H NMR δ ($CDCl_3$, 400 MHz) 1.54 (t, 3H, *J*=7.1 Hz, CH_3), 4.49 (q, 2H, *J*=7.1 Hz, CH_2), 4.90 (br s, 2H, NH_2), 7.64 (d, 1H, *J*=8.0 Hz, H-6), 7.80 (d, 1H, *J*=8.0 Hz, H-7); ^{13}C NMR δ ($CDCl_3$, 100.8 MHz) 14.29 (CH_3), 41.71 (CH_2), 125.42 (CH), 129.74 (CH), 130.70 (C), 130.81 (C), 132.94 (C), 136.45 (C), 139.79 (C), 141.93 (C), 146.69 (C); MS *m*/*z* (%) 283 (M^++2, 55), 281 (M^+, 86), 268 (64), 266 (100), 241 (18), 239 (27), 199 (15), 197 (31), 161 (19), 134 (16); IR (Nujol) 3285, 3160, 1633, 1607, 1566, 1394, 1199, 1180, 1122, 1090, 959, 938, 822, 696, 665 cm^{-1}.

*3.5.3. 3-Amino-5,8-dichloro-1-(2-hydroxyethyl)flavazole (**7c**).* Yield: 92%; crystallization from acetonitrile gave purple plates; mp 260–261 °C. (Found C 44.26; H 3.11; N 23.57; $C_{11}H_9Cl_2N_5O$ requires C 44.32; H 3.04; N 23.49); ^{1}H NMR δ (DMSO-d_6, 400 MHz): 3.87 (q, 2H, *J*=5.8 Hz, CH_2OH), 4.33 (t, 2H, *J*=5.8 Hz, CH_2), 4.75 (t, 1H, *J*=5.8 Hz, OH), 6.38 (br s, 2H, NH_2), 7.77 (d, 1H, *J*=8.1 Hz, H-6), 7.95 (d, 1H, *J*=8.1 Hz, H-7); ^{13}C NMR δ (DMSO-d_6, 100.8 MHz): 48.69 (CH_2), 58.61 (CH_2), 125.13 (CH), 129.39 (C), 129.86 (CH), 131.94 (C), 131.96 (C), 135.21 (C), 138.74 (C), 142.21 (C), 147.93 (C); MS *m*/*z* (%) 299 (M^++2, 51), 297 (M^+, 65), 268 (64), 266 (100), 253 (27), 239 (34), 212 (17), 197 (36), 170 (13), 161 (18), 134

(16); IR (Nujol) 3354, 3189, 1638, 1607, 1570, 1375, 1220, 1183, 1143, 1096, 1065, 1002, 938, 840, 820 cm^{-1}.

3.6. Preparation of 3-amino-1-aryl-5,8-dichloroflavazoles 8

To an ice-cooled solution of **3** (1.2 mmol) in dioxane (3 ml) a solution of the corresponding lithium arylhydrazinide 0.5 M in dioxane (1.26 mmol) was added dropwise under nitrogen, keeping the temperature below 10 °C. The mixture was stirred at rt for 16 h. Then, the reaction mixture was poured into an aqueous solution of ammonium chloride 10% (100 ml) and the suspension was extracted with ethyl acetate (2×75 ml). The organic layer was washed with water (100 ml) and dried over anhydrous magnesium sulfate. Then the solution was concentrated to dryness under reduced pressure and the solid obtained was crystallized in the appropriate solvent.

Lithium arylhydrazinide solutions were prepared a few minutes before being used by addition under nitrogen of a commercial 1.8 M LDA solution in heptane–tetrahydrofurane–ethylbenzene to a solution of the corresponding arylhydrazine in dioxane.

*3.6.1. 3-Amino-5,8-dichloro-1-phenylflavazole (**8a**).* Yield: 67%; crystallization from methanol gave red prisms; mp 226–228 °C. (Found C 54.69; H 2.69; N 21.28; $C_{15}H_9Cl_2N_5$ requires C 54.57; H 2.75; N 21.21); ^{1}H NMR δ (DMSO-d_6, 400 MHz) 6.91 (br s, 2H, NH_2), 7.23 (t, 1H, J=7.7 Hz, H-4′), 7.56 (t, 2H, J=7.7 Hz, H-3′,5′), 7.92 (d, 1H, J=8.1 Hz, H-6), 8.09 (d, 1H, J=8.1 Hz, H-7), 8.43 (d, 2H, J=7.7 Hz, H-2′,6′); ^{13}C NMR δ (DMSO-d_6, 100.8 MHz) 117.54 (CH), 123.99 (CH), 126.47 (CH), 129.18 (CH), 129.85 (C), 130.55 (CH), 132.01 (C), 134.39 (C), 135.74 (C), 138.72 (C), 139.22 (C), 141.25 (C), 149.36 (C); MS m/z (%) 331 (M^++2, 60), 329 (M^+, 100), 313 (4), 287 (12), 252 (6), 226 (7), 164 (11), 134 (6), 91 (15), 77 (38); IR (Nujol) 3329, 3183, 1597, 1567, 1505, 1393, 1262, 1196, 1117, 1092, 967, 941, 821, 751, 687 cm^{-1}.

*3.6.2. 3-Amino-5,8-dichloro-1-(4-methoxyphenyl)flavazole (**8b**).* Yield: 78%; crystallization from acetonitrile gave red plates; mp 191–193 °C. (Found C 52.48; H 3.01; N 19.37; $C_{16}H_{11}Cl_2N_5O$ requires C 53.35; H 3.08; N 19.44); ^{1}H NMR δ (DMSO-d_6, 400 MHz) 3.81 (s, 3H, OCH_3), 6.85 (br s, 2H, NH_2), 7.14 (d, 2H, J=9.2 Hz, H-3′,5′), 7.88 (d, 1H, J=8.1 Hz, H-6), 8.06 (d, 1H, J=8.1 Hz, H-7), 8.29 (d, 2H, J=9.2 Hz, H-2′,6′); ^{13}C NMR δ (DMSO-d_6, 100.8 MHz) 55.33 (CH_3), 114.40 (CH), 119.19 (CH), 126.16 (CH), 129.75 (C), 130.48 (CH), 132.05 (C), 132.64 (C), 134.04 (C), 135.57 (C), 138.84 (C), 140.62 (C), 149.11 (C), 155.97 (C); MS m/z (%) 361 (M^++2, 66), 359 (M^+, 100), 346 (47), 344 (68), 316 (9), 302 (6), 179 (7), 92 (6), 78 (20); IR (Nujol) 3308, 1605, 1565, 1513, 1301, 1246, 1195, 1175, 1033, 969, 943, 824 cm^{-1}.

*3.6.3. 3-Amino-1-(4-tert-butylphenyl)-5,8-dichloroflavazole (**8c**).* Yield: 63%; crystallization from methanol gave red prisms; mp 230–233 °C. (Found C 59.21; H 4.51; N 18.02; $C_{19}H_{17}Cl_2N_5$ requires C 59.08; H 4.44; N 18.13); ^{1}H NMR δ (DMSO-d_6, 400 MHz) 1.34 (s, 9H, $C(CH_3)_3$), 6.73 (br s, 2H, NH_2), 7.57 (d, 2H, J=8.9 Hz, H-3′,5′), 7.88 (d, 1H, J=8.1 Hz, H-6), 8.05 (d, 1H, J=8.1 Hz, H-7), 8.32 (d, 2H, J=8.9 Hz, H-2′,6′); ^{13}C NMR δ (DMSO-d_6, 100.8 MHz) 30.96 (CH_3), 33.94 (C), 117.35 (CH), 125.56 (CH), 126.10 (CH), 129.69 (C), 130.24 (CH), 131.85 (C), 133.86 (C), 135.56 (C), 136.56 (C), 138.63 (C), 140.84 (C), 146.45 (C), 148.99 (C); MS m/z (%) 387 (M^++2, 22), 385 (M^+, 33), 372 (63), 370 (100), 355 (11), 211 (6), 185 (9), 171 (39), 115 (30); IR (Nujol) 3327, 1609, 1567, 1519, 1267, 1191, 1094, 973, 944, 834, 812, 667 cm^{-1}.

3.7. Preparation of 5,8-dichloro-3-hydrazino-2-quinoxalinylcarboxamidrazone 9

To a solution of **3** (2 mmol) in THF (10 ml) a solution of aqueous hydrazine (55%; 2 ml) and triethylamine (2.2 mmol) in THF (5 ml) was added dropwise. The mixture was stirred at rt for 2 h. Then, the solvent was concentrated to dryness under reduced pressure and the solid obtained was washed with water, collected by filtration and crystallized from acetonitrile.

Yield: 96%; crystallization from acetonitrile gave yellow needles; mp 287–296 °C (dec). (Found C 37.93; H 3.30; N 34.39; $C_9H_9Cl_2N_7$ requires C 37.78; H 3.17; N 34.27); ^{1}H NMR δ (DMSO-d_6, 400 MHz) 4.88 (br s, 2H, NH_2), 5.95 (br s, 2H, NH_2), 6.17 (br s, 2H, NH_2), 7.41 (d, 1H, J=8.2 Hz, H-7), 7.65 (d, 1H, J=8.2 Hz, H-6), 10.55 (br s, 1H, NH); ^{13}C NMR δ (DMSO-d_6, 100.8 MHz) 122.69 (CH), 126.34 (C), 129.02 (CH), 129.98 (C), 131.21 (C), 134.13 (C), 138.43 (C), 143.19 (C), 150.30 (C); MS m/z (%) 287 (M^++2, 33), 285 (M^+, 52), 256 (63), 254 (100), 241 (13), 224 (13), 213 (14), 198 (12), 171 (9), 149 (8), 136 (6); IR (Nujol) 3425, 3355, 3295, 3161, 1638, 1556, 1497, 1320, 1234, 1195, 1154, 1109, 993, 946, 857, 822, 809, 794, 668 cm^{-1}.

3.8. Preparation of 3-amino-5,8-dichloroflavazole 10

Solid 5,8-dichloro-3-hydrazino-2-quinoxalinylcarboxamidrazone **9** was heated at 200 °C under vacuum for 15 min. Crude 3-amino-5,8-dichloroflavazole **10** (a red solid) was purified by crystallization in ethanol.

Yield: 83%; crystallization from ethanol gave red needles; mp 293–295 °C. (Found C 42.67; H 2.00; N 27.63; $C_9H_5Cl_2N_5$ requires C 42.54; H 1.98; N 27.56); ^{1}H NMR δ (DMSO-d_6, 400 MHz) 6.21 (br s, 2H, NH_2), 7.80 (d, 1H, J=8.1 Hz, H-6), 7.96 (d, 1H, J=8.1 Hz, H-7), 12.67 (s, 1H, NH); ^{13}C NMR δ (DMSO-d_6, 100.8 MHz) 125.34 (CH), 129.55 (C), 129.66 (CH), 131.37 (C), 131.97 (C), 135.41 (C), 138.74 (C), 143.29 (C), 148.53 (C); MS m/z (%) 255 (M^++2, 66), 253 (M^+, 100), 211 (13), 198 (28), 170 (15), 161 (11), 149 (20); IR (Nujol) 3455, 3315, 1619, 1579, 1555, 1276, 1199, 1128, 1092, 958, 940, 824, 690, 667 cm^{-1}.

3.9. Preparation of 3-[*N*,*N*-bis(4-chlorobenzoyl)amino]-5,8-dichloro-1-phenylflavazole 11

To a solution of **8a** (1 mmol) and triethylamine (10 mmol) in dichloromethane (15 ml) a solution of *p*-chlorobenzoyl chloride (10 mmol) in dichloromethane (6 ml) was added dropwise. The mixture under nitrogen was stirred at rt for 12 h. Then the solution was washed twice with aqueous solution of sodium bicarbonate 5% (30 ml). The organic layer was dried over anhydrous magnesium sulfate and concentrated to dryness under reduced pressure. The solid obtained was crystallized in acetonitrile.

Yield: 95%; crystallization from acetonitrile gave orange needles; mp 221–223 °C; ^{1}H NMR δ (DMSO-d_6, 300 MHz) 7.34–7.37 (m, 5H), 7.57 (t, 2H, J=7.7 Hz), 7.81–7.88 (m, 5H), 7.94 (d, 1H, J=8.1 Hz), 8.39 (d, 2H, J=7.7 Hz); ^{13}C NMR δ (DMSO-d_6, 75.4 MHz) 119.75 (CH), 126.61 (CH), 128.14 (CH), 129.13 (CH), 129.40 (CH), 130.59 (CH), 130.80 (CH), 131.69 (C), 132.11 (C), 133.34 (C), 138.48 (C), 138.80 (C), 139. 47 (C), 139.51 (C), 141.72 (C), 141.84 (C), 170.93 (C); HRMS (ESI) m/z: calcd for $C_{29}H_{15}Cl_4N_5O_2$: 604.9980, found: 604.9968; IR (Nujol) 3467, 2958, 2924, 2853, 1704, 1590, 1568, 1504, 1473, 1431, 1356, 1256, 1243, 1191, 1092, 1013, 969, 946, 919, 871, 847, 801, 760, 748, 729, 684, 673 cm^{-1}.

3.10. X-ray structure determination of compound 11

Crystal data: $C_{30}H_{16}Cl_7N_5O_2$, M_r=726.63, triclinic, space group $P\bar{1}$, a=9.3816(5), b=10.1595(5), c=16.6314(9) Å, α=91.319(2)°, β=91.806(2)°, γ=106.854(2)°, V=1515.48(14) Å^3 at −173 °C; Z=2, D_x=1.592 g cm^{-3}, F(000)=732, μ=0.69 mm^{-1}. *Data collection*: A yellow lath 0.32×0.13×0.06 mm was mounted in inert oil on a glass fibre and transferred to the cold gas stream of the diffractometer (Bruker SMART APEX CCD). Measurements were performed to $2\theta_{max}$ 56° with monochromated Mo $K\alpha$ radiation. Of 16,911 measured reflections, 6778 were unique (R_{int}=0.0256) and were used for all calculations. *Structure refinement*: The structures were refined anisotropically against F^2 (program SHELXL-97)[51] The

hydrogen atoms were refined using a riding model. The final *wR*2 value was 0.1105 for all reflections and 397 parameters, with *R*1 0.0448 for reflections with $I>2\sigma(I)$; max. $\Delta\rho$ 0.57 e/Å^3, *S* 1.052.

Complete crystallographic data (excluding structure factors) have been deposited at the Cambridge Crystallographic Data Centre under the number CCDC 809717. Copies may be requested free of charge from The Director, CCDC, 12 Union Road, Cambridge CB2 1EZ, England (E-mail: deposit@ccdc.cam.ac.uk).

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Supplementary data

X-ray structural data of compound **11**. ^{13}C and ^{1}H NMR spectra of compounds **4**–**11**. Supplementary data related to this article can be found online at doi:10.1016/j.tet.2011.03.104.

References and notes

1. Heydenreich, M.; Koch, A.; Sarodnick, G.; Kleinpeter, E. *Tetrahedron* **2005**, *61*, 2373.
2. Alkorta, I.; Elguero, J. *J. Phys. Org. Chem.* **2005**, *18*, 719.
3. Ortega, M.; Montoya, M.; Zarranz, B.; Jaso, A.; Aldana, I.; Leclerc, S.; Meijer, L.; Monge, A. *Bioorg. Med. Chem.* **2002**, *10*, 2177.
4. Mellman, I.; Jiang, A. WO 07,591,1A2, 2007.
5. Aguirre, G.; Cerecetto, H.; Di Maio, R.; Gonzalez, M.; Alfaro, M. E. M.; Jaso, A.; Zarranz, B.; Ortega, M. A.; Aldana, I.; Monge-Vega, A. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 3835.
6. Sarodnick, G.; Heydenreich, M.; Linker, T.; Kleinpeter, E. *Tetrahedron* **2003**, *59*, 6311.
7. Makino, K.; Kim, H.; Kurasawa, Y. *J. Heterocycl. Chem.* **1999**, *36*, 321.
8. Shawali, A. S.; Zayed, M. M.; Farghaly, T. A. *J. Heterocycl. Chem.* **2005**, *42*, 185.
9. Ponizovsky, M. G.; Boguslavsky, A. M.; Kodess, M. I.; Charushin, V. N.; Chupakhin, O. N. *Mendeleev Commun.* **2002**, 68.
10. Abbasi, M. M.; El-Kousy, S. M.; El-Moghazy, Y. E.; El-Kafrawy, S. *Int. J. Chem.* **2005**, *15*, 77.
11. Awad, L. F. *Carbohydr. Res.* **2000**, *326*, 34.
12. Mac, M.; Danel, A.; Wisla, A.; Karocki, A.; Krolicki, R. *J. Photochem. Photobiol., A* **2006**, *180*, 88.
13. Gondek, E.; Kityk, I. V.; Danel, A.; Wisla, A.; Pokladko, M.; Sanetra, J.; Sahraoui, B. *Mater. Lett.* **2006**, *60*, 3301.
14. Lee, S.; Lee, C.; Wang, P.; Xie, Z. U.S. Patent 00,43,24,7A1, 2004.
15. Wang, P.; Xie, Z.; Hong, Z.; Tang, J.; Wong, O.; Lee, C.-S.; Wong, N.; Lee, S. *J. Mater. Chem.* **2003**, *13*, 1894.
16. Kucybala, Z.; Kosobucka, A.; Paczkowski, J. *J. Photochem. Photobiol. A: Chem.* **2000**, *136*, 227.
17. Pfluecker, F.; Schwarz, M.; Scholz, V.; Neunhoeffer, H. U.S. Patent 7,10,153,7B2, 2006.
18. Monge, A.; Palop, J. A.; Pinol, A.; Martinez-Crespo, F. J.; Narro, S.; Gonzalez, M.; Sainz, Y.; Lopez de Cerain, A.; Hamilton, E.; Barker, A. J. *J. Heterocycl. Chem.* **1994**, *31*, 1135.
19. Monge, A.; Palop, J. A.; Ochoa de Retana, A.; Urbasos, I.; Fernandez Alvarez, E. *An. Quim., Ser. C* **1988**, *84*, 364.
20. Yoshida, K.; Otomasu, H. *Chem. Pharm. Bull.* **1984**, *32*, 3361.
21. Henseke, G.; Sauer, W. DD 83,361, 1971.
22. Ortega, M. A.; Morancho, M. J.; Martinez-Crespo, F. J.; Sainz, Y.; Montoya, M. E.; De Cerain, A. L.; Monge, A. *Eur. J. Med. Chem.* **2000**, *35*, 21.
23. Monge, A.; Palop, J. A.; de Cerain, A. L.; Senador, V.; Martinez, F. J.; Sainz, Y.; Narro, S.; Garcia, E.; de Miguel, C. *J. Med. Chem.* **1995**, *38*, 1786.
24. Monge, A.; Martinez-Crespo, F. J.; Lopez de Cerain, A.; Palop, J. A.; Narro, S.; Senador, V.; Marin, A.; Sainz, Y.; Gonzalez, M. *J. Med. Chem.* **1995**, *38*, 4488.
25. Monge, A.; Palop, J. A.; Del Castillo, J. C.; Caldero, J. M.; Roca, J.; Romero, G.; Del Rio, J.; Lasheras, B. *J. Med. Chem.* **1993**, *36*, 2745.
26. Charushin, V. N.; Kotovskaya, S. K.; Perova, N. M.; Chupakhin, O. N. *Mendeleev Commun.* **2001**, 54.
27. Montoya, M. E.; Sainz, Y.; Ortega, M. A.; De Cerain, A. L.; Monge, A. *Farmaco* **1998**, *53*, 570.
28. Ribeiro da Silva, M.; Gomes, J.; Goncalves, J. M.; Sousa, E. A.; Pandey, S.; Acree, J. *Org. Biomol. Chem.* **2004**, *2*, 2507.
29. Haldar, P.; Dutta, B.; Guin, J.; Ray, J. *Tetrahedron Lett.* **2007**, *48*, 5855.
30. Pillai, P. M.; Ramabhadran, P. *Indian J. Chem.* **1986**, *25B*, 960.
31. Kurasawa, Y.; Muramatsu, M.; Yamazaki, K.; Tajima, S.; Okamoto, Y.; Takada, A. *J. Heterocycl. Chem.* **1986**, *23*, 633.
32. Kurasawa, Y.; Muramatsu, M.; Yamazaki, K.; Tajima, S.; Okamoto, Y.; Takada, A. *J. Heterocycl. Chem.* **1986**, *23*, 959.
33. Kurasawa, Y.; Muramatsu, M.; Yamazaki, K.; Tajima, S.; Okamoto, Y.; Takada, A. *J. Heterocycl. Chem.* **1986**, *23*, 1391.
34. Kurasawa, Y.; Muramatsu, M.; Yamazaki, K.; Tajima, S.; Okamoto, Y.; Takada, A. *J. Heterocycl. Chem.* **1986**, *23*, 1379.
35. Kurasawa, Y.; Yamazaki, K.; Tajima, S.; Okamoto, Y.; Takada, A. *J. Heterocycl. Chem.* **1986**, *23*, 281.
36. Guirado, A.; López-Sánchez, J. I.; Cerezo, A.; Bautista, D.; Gálvez, J. *Tetrahedron* **2009**, *65*, 2254.
37. Guirado, A.; Cerezo, A.; López-Sánchez, J. I.; Bautista, D. *Tetrahedron Lett.* **2007**, *48*, 9137.
38. Guirado, A.; Cerezo, A.; Andreu, R.; López-Sánchez, J. I.; Bautista, D. *Tetrahedron* **2004**, *60*, 6747.
39. Guirado, A.; Cerezo, A.; Andreu, R. *Tetrahedron Lett.* **2000**, *41*, 6579.
40. Guirado, A.; Cerezo, A.; Ramírez de Arellano, C. *Tetrahedron* **1997**, *53*, 6183.
41. Bird, C.; Cheeseman, G.; Sarsfield, A. *J. Chem. Soc.* **1963**, 4767.
42. Boulton, A.; Gripper Gray, A.; Katritzky, A. *J. Chem. Soc. B* **1967**, 909.
43. Mallory, F.; Manatt, S.; Wood, C. *J. Am. Chem. Soc.* **1965**, *87*, 5433.
44. Pillai, P. M.; Bhat, V. S. *Indian J. Chem.* **1989**, *28B*, 1026.
45. Guirado, A.; Cerezo, A.; López-Sánchez, J. I.; Sáez-Ayala, M.; Bautista, D. *Tetrahedron Lett.* **2006**, *47*, 7583.
46. Rothkopf, H.; Wöhrle, D.; Müller, R.; Kobmehl, G. *Chem. Ber.* **1975**, *108*, 875.
47. Brown, D. In *Quinoxalines*; Taylor, E., Wipf, P., Weissberger, A., Eds.; John Wiley and Sons: New Jersey, 2006.
48. Ahmad, A.; Mehta, L.; Parrick, J. *J. Chem. Soc., Perkin Trans. 1* **1996**, 2443.
49. Caldero, J. M.; Monge, A.; Del Rio, J.; Palop, J. A.; Lasheras, B.; Del Castillo, J. C.; Roca, J.; Bosch, A. ES 20,42,395, 1993.
50. Gobec, S.; Urleb, U. *Sci. Synth.* **2006**, *16*, 845.
51. Sheldrick, G. M. *Acta Crystallogr.* **2008**, *A64*, 112.