HETEROCYCLES, Vol. 68, No. 4, 2006, pp. 787 - 799. © The Japan Institute of Heterocyclic Chemistry
Received, 4th January, 2006, Accepted, 6th March, 2006, Published online, 7th March, 2006. COM-06-10665

SYNTHESIS OF 3-CYANOFLAVONES AND THEIR BIOLOGICAL EVALUATION

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Abstract-The synthesis, using β-bromo-α-ethylthiocinnamonitrile (**1**) and methyl salicylate (**2**)**,** of two new series of methyl 2-(2'-cyano-2'-ethylthio-1'-phenylvinyloxy)benzoates (**3**), precursors of 3-cyanoflavones (**4**) is reported. Compounds (**3**) and (**4**) were checked against representatives Gram-positive and -negative bacteria (*Escherichia coli, Staphylococcus aureus* and *Enterococcus hirae).* These compounds were quite inactive against bacteria, which is not the case for the two fungi strains investigated (*Candida albicans* and *Saccharomyces cerevisiae*). The presence of a 4'-substituent on the 3-cyanoflavone skeleton gives a different effect for *S. cerevisiae*. The presence of a methylendioxy substituent on the methyl 2-(2'-cyano-2'-ethylthio-1'-phenylvinyloxy)benzoates (**3**) enhance the effect in particular for *C. albicans.*

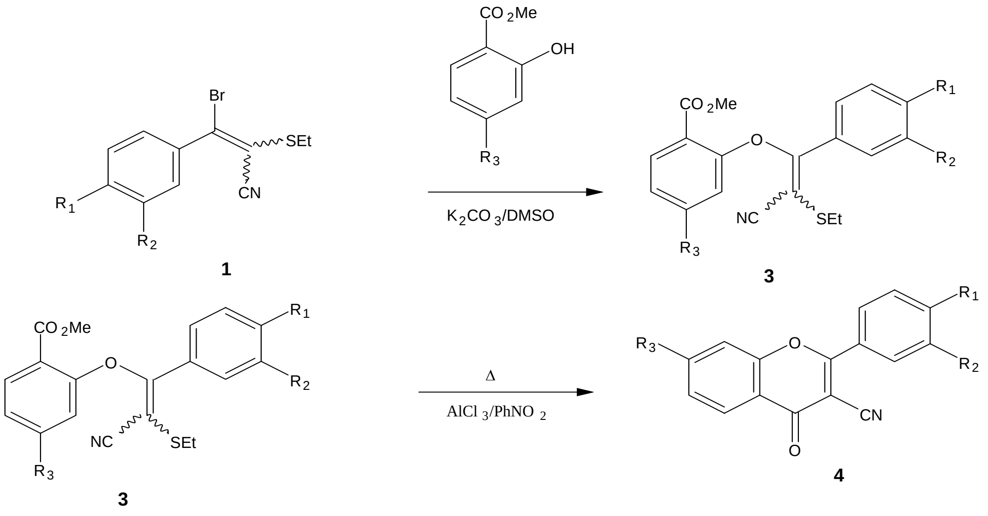
INTRODUCTION

Flavones comprise a large group of common plant metabolites. It appears that they are secondary metabolites involved in the plant growth hormone and growth regulators in defence against infection. They exhibit a wide range of biochemical and physiological activities towards other life forms[1] such as viruses,[2-5] fungi[6-7] and bacteria.[8-12] Quercetin, 3,5,7,3',4'-pentahydroxyflavone, has been proven to be toxic for *Candida tropicalis*[13] and *C. albicans*[14] in a concentration between 50 and 100 µg mL^{-1}. Quercetin 3-α-L-arabinopyranoside-2''-gallate appeared to have a potent antibacterial activity in nutritional agar medium at a concentration of 100 µg mL^{-1} against *Escherichia coli.*[15] 5,7,4'-Trihydroxy-3,8-dimethoxyflavone was shown to be active against *Bacillus cereus.*[16] Although the effectiveness of various antibiotics was about 20 fold higher than quercetin against *Staphylococcus aureus, Enterobacter aerogenes* and *E. coli,*[13] the rising prevalence of multi-drug resistant fungi and bacteria continues to provides the search and discovery of new antimicroorganism agents active against these pathogens.

Therefore, for more efficient control, new series of flavones derivatives, active against the tested microorganisms have been investigated, such as flavonyl oxime ether derivatives,[17] amino substituted flavones,[18] or 3-bromoflavones.[19] Since literature data show that C-3 substituted flavones play an important role in various biological processes and as a continuation of our program on 3-cyanoflavones and their precursors,[20] we synthesized new compounds and evaluated in vitro their antifungal and antibacterial activities.

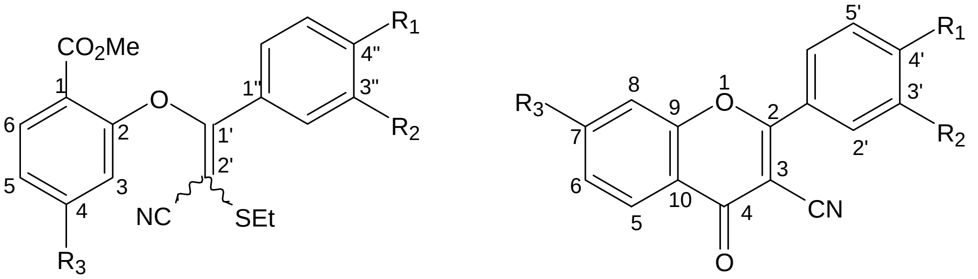
RESULTS AND DISCUSSION

Among the numerous C-3 functionalized flavones described in the literature,[21] few examples of 3-cyanoflavones have been recently reported as by-product from a reaction starting from 3-α-hydroxybenzylflavone.[22] This way to access to 3-cyanoflavones remain difficult and yields are somewhat low. During the course of our research, we found a new route to 3-cyanoflavones (**4**)[20] using β-bromo-α-ethylthiocinnamonitrile (**1**) (Scheme 1).



Scheme 1. General method leading to 3-cyanoflavones (**4**)

Bromo compounds (**1**) which are obtained from an aromatic aldehyde and ethylthioacetonitrile, with good yields (70-80%) following a previously described method,[23] react in alkaline medium (K_2CO_3/DMSO) with methyl salicylate (**2**)[24,25] to give methyl 2-(2'-cyano-2'-ethylthio-1'-phenylvinyloxy)benzoates (**3**) as *Z, E* mixtures, the precursors of 3-cyanoflavones (**4**) in fair yields. Synthesis of precursors (**3a**) to (**3l**) (Figure 1 and Scheme 1), led to *Z* and *E* conformers in 80% and 20% yields respectively (relative percentage determined by ^{1}H NMR spectral signal of the ethylthio methylene group).



3 **4**

3a	$R_1 = R_2 = R_3 = H$	**4a**	$R_1 = R_2 = R_3 = H$
3b	$R_1 =Cl; R_2 = R_3 = H$	**4b**	$R_1 = Cl; R_2 = R_3 = H$
3c	$R_1 = Me; R_2 = R_3 = H$	**4c**	$R_1 = Me; R_2 = R_3 = H$
3d	$R_1 = t$Bu; $R_2 = R_3 = H$	**4d**	$R_1 = t$Bu; $R_2 = R_3 = H$
3e	$R_1 = OMe; R_2 = R_3 = H$	**4e**	$R_1 = OMe; R_2 = R_3 = H$
3f	R_1 and $R_2 = OCH_2O; R_3 = H$		
3g	$R_1 = R_2 = H; R_3 = OMe$	**4g**	$R_1 = R_2 = H; R_3 = OMe$
3h	$R_1 = Cl; R_2 = H; R_3 = OMe$	**4h**	$R_1 = Cl; R_2 = H; R_3 = OMe$
3i	$R_1 = CH_3; R_2 = H; R_3 = OMe$	**4i**	$R_1 = CH_3; R_2 = H; R_3 = OMe$
3j	$R_1 = t$Bu; $R_2 = H; R_3 = OMe$	**4j**	$R_1 = t$Bu; $R_2 = H; R_3 = OMe$
3k	$R_1 = OMe; R_2 = H; R_3 = OMe$	**4k**	$R_1 = OMe; R_2 = H; R_3 = OMe$
3l	R_1 and $R_2 = OCH_2O; R_3 = OMe$	**4l**	R_1 and $R_2 = OCH_2O; R_3 = OMe$

Figure 1. Structures of Methyl 2-(2'-Cyano-2'-ethylthio-1'-phenylvinyloxy)benzoates (**3**) and 3-Cyanoflavones (**4**). Carbon numbering in ^{1}H and ^{13}C NMR spectrum.

In fact, the magnetic anisotropic effect of aromatic ring shielded the methylene signal of the ethylthio group in *E*-**3a** isomers and deshielded the methylene signal of the ethylthio group in *Z*-**3a** isomers. Yields (mixture of *Z* and *E* conformers) and melting points are given in Table 1. For compound (**3a**), isomers *Z* and *E* were separated by sequential crystallization of crude mixture in ether since *E*-**3a,** the minor product, was less soluble in ether. Cyanoflavones (**4**) were obtained from (**3**) in moderate yields (27-65%) and were purified by column chromatography (CC) using methylene chloride/ ethyl acetate (Table 1, Figure 1 and Scheme 1).

Table 1. Experimental data of precursors (3) and 3-cyanoflavones (4).

Precursor Z/E mixture in ratio 80:20	Mp (°C)	Recrystallization solvent	Yield (%)	**Flavone**	CC eluent (v/v) CH_2Cl_2/AcOEt	R_f	Mp (°C)	Yield (%)
3a	58-68	Ether	85	**4a**	100/0	0.45	157-158	54
3b	90-92	Ethyl alcohol	84	**4b**	97.5/2.5	0.35	210-212	42
3c	-	-	75	**4c**	99/1	0.34	196	40
3d	92-94	Petroleum ether	70	**4d**	99/1	0.40	185-186	44
3e	-	-	75	**4e**	97.5/2.5	0.26	176-178	27
3f	-	-	75	**4f**	-	-	-	-
3g	64-70	Petroleum ether	86	**4g**	97.5/2.5	0.26	209-210	64
3h	80-94	Methyl alcohol	70	**4h**	97/3	0.31	221-222	65
3i	76-80	Cyclohexane	75	**4i**	98/2	0.23	182-183	61
3j	128-132	Pentane	70	**4j**	97/3	0.30	174-173	60
3k	90-100	Methyl alcohol	81	**4k**	95/5	0.36	224-225	63
3l	100-110	Ethyl alcohol	85	**4l**	95/5	0.45	269-270	35

Cyclization conditions for precursor (**3**) were optimized using various solvents (methylene chloride, nitromethane, nitrobenzene) and different Lewis acids ($ZnCl_2$, $SnCl_4$, BF_3, $AlCl_3$). A complete conversion of **3a** to **3l** into 3-cyanoflavones (**4a** to **4l**) was obtained with nitrobenzene as solvent (150°C) and $AlCl_3$ (3.1 equivalents) and these experimental conditions were generalized flavone (**4f**) could never be obtained). Using the other experimental conditions, no reaction occurred, or a mixture of unreacted precursors (**3**), resins and methyl salicylate were recovered. The presence of *Z* and *E* diastereoisomers did not affect the cyclization reaction of **3**. In fact synthesis of **4a** starting from *Z*-**3a** or *E*-**3a** separately gave 3-cyanoflavone (**4a**) with the same yield, showing therefore that the cyclization did not depend on the stereochemistry of the double bond. Flavone (**4e**) has been reported by Mallik *et al.*[22] as a by-product from a reaction using 3-α-hydroxybenzylflavone but with a lower yield. The higher yields for 3-cyanoflavones (**4**) were obtained when R_3 is a methoxy group except for **4l** (Table 1). The ^{1}H chemical shifts of precursors (**3**) and 3-cyanoflavones (**4**) are given in EXPERIMENTAL.

BACTERICIDAL AND FUNGICIDAL ACTIVITIES

The 3-cyanoflavones and their precursors were tested for bactericidal and fungicidal activities. The different molecules tested don’t affect significantly the bacteria (*Escherichia coli* CIP 54 127, *Enterococcus hirae* CIP 58 55 and *Staphylococcus aureus* CIP 53 154) while some of them can partially inhibit the fungi (*Candida albicans* CIP 1180-79 and *Saccharomyces cerevisiae* ATCC 28383). No real fungicidal action was observed but a fungistatic effect. The 50 % antifungal inhibitory concentration values (IC_{50}, in µg/mL) were determinated after 36 hours incubation for fungi (Table 2).

Table 2 : IC_{50} (µg/mL) values of compounds (3a-f, 3l[a] and 4a,b,d,g,h,j,l[b]) against *Candida albicans* and *Saccharomyces cerevisiae.*

Compound[c]	*Candida albicans (*CIP 1180-79)	*Saccharomyces cerevisiae (*ATCC 28 383)
Penicillin G	0.15	0.15
3a	-	50
3b	100	50
3c	12.5	25
3d	50	-
3e	-	25
3f	1.6	100
3l	6.25	100
4a	-	25
4b	50	100
4d	6.25	50
4g	100	100
4h	50	-
4j	6.25	-
4l	-	100

[a] For compounds (**3g**, **3h**, **3i**, **3j** and **3k**) no significant effects were observed.

[b] For compounds (**4c**, **4e**, **4i**, and **4k**) no significant effects were observed.

[C] Test compounds (**3a** to **3l**) are Z/E mixture in ratio 80:20.

Compounds (**3d, 4h** and **4j**) exhibit fungistatic effect *only* against *C. albicans* whereas compounds (**3a, 3e, 4a** and **4l**) exhibit fungistatic effect against *S. cerevisiae.*

Compounds (**3b, 3c, 3f, 3l, 4b, 4d** and **4g**) exhibit activitiy against *C. albicans* and *S. cerevisiae* with a higher effect against *C. albicans* for all these components except for **3b** and **4g**. Compounds (**3f**) (R_1 and R_2= OCH_2O; R_3 = H) exhibit the most potent antifungal activity against *C. albicans* (IC_{50} at 1.6 µg/mL). A total inhibition was observed for compound (**4b**) (R_1 = Cl; R_2 = R_3 = H) against *C. albicans* at a concentration of 100 µg/mL. The presence of a methylene dioxy substituent on methyl 2-(2’-cyano-2’-

ethylthio-1’-phenylvinyloxy)benzoates (**3**) enhance the effect in particular for *C. albicans* whereas the presence of a methoxy group on the 4 position (R_3=OMe) give a lower activity. The results showed that the presence of a substituent on the 4’ position of the 3-cyanoflavone skeleton give a lower effect on *S. cerevisiae*. In fact, the highest activity on *S. cerevisiae* was observed for 3-cyanoflavone (**4a**) (R_1=R_2=R_3=H). Furthermore, the presence of a methoxy group on the 7 position (R_3=OMe) of the 3-cyanoflavones gave a lower activity against *S. cerevisiae* if we compare **4a** to **4g**, **4b** to **4h** or **4d** to **4i**. This effect was not observed for *C. albicans.*

EXPERIMENTAL

Chemistry

Melting points (°C) were determined with a Koffler apparatus and are uncorrected. NMR spectra were recorded on Bruker spectrometers, 75 MHz for ^{13}C and 200 MHz for ^{1}H or 500 MHz for the ^{1}H of the two **3a** *Z* and *E* isomers. The NMR spectra were measured as solutions in chloroform-*d* in 5 mm o.d. tubes for ^{13}C and ^{1}H. Tetramethylsilane was used as internal standard in both measurements. Proton-proton coupling constants were extracted from high-field resolution-enhanced ^{1}H spectra using the gaussian multiplication technique.[26]

General procedure for synthesis of 2-(2-cyano-2-(ethylthio-1-arylvinyloxy))benzoates (3a-3l)

β-Bromo-α-ethylthiocinnamonitrile[23] (**1**) (6 mmol) and methyl salicylate (7.2 mmol) were added to a solution of anhydrous potassium carbonate (6.5 mmol) in dry DMSO (10 mL). The mixture was stirred overnight at 70-80°C. After pouring into cold water, ether extraction and washing with 1 mol.L^{-1} NaOH aqueous solution, compounds (**3**) (*Z/E* mixture) were isolated in good yields (70-90%) as shown in Table 1. Compounds (**3a**,**b**,**d**,**g-l**) were purified by recrystallization (Table 1) before spectral analyses. For compound (**3a**), isomers *Z* and *E* were separated by sequential crystallization of crude mixture in ether (TLC: eluent CH_2Cl_2/petroleum ether (80:20, v/v), *E*-**3a** (R_f 0.41) and *Z*-**3a** (R_f 0.29)). Experimental data of compounds (**3**) are given in Table 1.

General procedure for synthesis of 3-cyanoflavones (4a-4l)

To a stirred solution of precursor (**3**) (1.5 mmol) in dry nitrobenzene (50 mL) at 150 °C (inner temp.) was added dropwise, over 2-3 min, a nitrobenzene solution of $AlCl_3$ (0.88 mol.L^{-1}, 5.3 mL). After stirring for a further 5 min at the same temperature, the mixture was poured into cold 10% HCl aqueous solution, extracted with CH_2Cl_2 and washed with 5% aqueous sodium hydrogenocarbonate and water until neutral pH. The organic layer was dried over $CaCl_2$ and filtered over celite. The solvents were removed and residual solid was purified on a silica gel column (silica gel 60 F_{245}, 230-400 mesh, 15 g) eluted with

CH_2Cl_2 / AcOEt in the range 90:10 to 98:2 (v/v). Spots were visualized by examination under UV light at 254 nm. Experimental data of compounds (**4**) are given in Table 1.

^{1}H and ^{13}C NMR data, MS spectroscopy of compounds (3a-l) and (4a-l) and microanalysis of compounds (4a-l).

(*Z*)-3a : δ 7.82 (1H, dd, *J*=7.90 and 1.35 Hz, H-6), 7.67 (2H, dd, *J*=7.50 and 1.28 Hz, H-2", 6"), 7.30 (4H, m, H-3", 5", 4, 5), 7.04 (1H, t, *J*=7.90 Hz, H-4"), 6.70 (1H, d, *J*=8.3 Hz, H-3), 3.96 (3H, s, OMe), 2.98 (2H, q, *J*=7.4 Hz), 1.38 (3H, t, *J*=7.4 Hz).

(*E*)-3a : δ 7.80 (1H, dd, *J*=7.8 and 1.7 Hz, H-6), 7.60 (2H, dd, *J*=7.9 and 1.68 Hz, H-2",6"), 7.30 (4H, m, H-3",5",4,5), 7.03 (1H, dt, *J*=7.9 and 0.94 Hz, H-4"), 6.80 (1H, d, *J*=8.3 Hz, H-3), 3.95 (3H, s, OMe), 2.86 (2H, q, *J*=7.4 Hz), 1.29 (3H, t, *J*=7.4 Hz). EIMS: *m/z* found 339.0919 (M$^+$). calcd for $C_{19}H_{17}NO_3S$: 339.0929 (M$^+$). δ^{13}C : 121.50 (C1) 153.62 (C2) 116.11 (C3) 131.48 (C4) 124.46 (C5) 131.34 (C6) 164.84 (C1') 94.28 (C2') 120.00 (2'-CN) 165.05 ($\underline{C}OOCH_3$) 52.58 ($COO\underline{C}H_3$) 27.39 ($S\underline{C}H_2CH_3$) 15.15 ($SCH_2\underline{C}H_3$) 134.01 (1'') 128.90 (2'')129.03 (3'')130.96 (4'')129.03 (5'')128.90 (6'').

4a : δ 8.30 (1H, dd, *J*=8.1 and 1.5 Hz, H-5), 8.10-8.20 (2H, m, H-2', 6'), 7.80-7.90 (1H, ddd, *J*=7.50, 7.20 and 1.5 Hz, H-7), 7.60-7.70 (4H, m, Ar-H), 7.50-7.60 (1H, dt, *J*=7.6 and 1.0 Hz, H-6). δ^{13}C : 172.13 (C2) 98.53 (C3) 174.89 (C4) 134.15 (C5) 125.90 (C6) 136.63 (C7) 119.80 (C8) 156.06 (C9) 122.27 (C10) 115.41 (3-CN) 131.04 (C1') 129.74 (C2') 129.90 (C3') 127.91(C4') 129.90 (C5') 129.74 (C6'). EIMS: *m/z* found 247.0623 (M$^+$). calcd for $C_{16}H_9NO_2$: 247.0633 (M$^+$). Anal. Calcd for $C_{16}H_9NO_2$: C, 77.72; H, 3.67; N, 5.57. Found : C, 77.68; H, 3.65; N, 5.56.

3b : δ 7.85 (1H, dd, *J*=7.8 and 1.8 Hz, H-6), 7.60-7.70 (2H, d, *J*=8.6 Hz, H-2", 6"), 7.20-7.40 (3H, m, H-4, 3", 5"), 7.05 (1H, t, *J*=7 Hz, H-5), 7.20-7.30 (1H, dd, *J*=7.2 and 1 Hz, H-3), 3.98 (3H, s), 2.80-3.00 (2H, q, *J*=7.4 Hz), 1.20-1.40 (3H, t, *J*=7.4 Hz). EIMS: *m/z* found 373.0524 (M$^+$). calcd for $C_{19}H_{16}NO_3ClS$: 373.0539 (M$^+$). δ^{13}C : 124.67 (C1) 153.45 (C2) 119.99 (C3) 131.55 (C4) 128.69 (C5) 129.83 (C6) 163.23 (C1') 95.21 (C2') 121.49 (2'-CN) 165.02 ($\underline{C}OOCH_3$) 52.64 ($COO\underline{C}H_3$) 27.39 ($S\underline{C}H_2CH_3$) 15.17 ($SCH_2\underline{C}H_3$) 136.09 (C1'') 129.12 (C2'') 130.86 (C3'') 134.14 (C4'') 130.86 (C5'') 129.12 (C6'')

4b : δ 8.27 (1H, dd, *J*=7.9 and 1.7 Hz, H-5), 7.10 (2H, d, *J*=8.5 Hz, H-2', 6'), 7.80 (1H, t, *J*=7.9 Hz, H-7), 7.60 (2H, d, *J*=8.5 Hz, H-3', 5'), 7.50-7.65 (2H, m, H-6, 8). δ^{13}C : 174.12 (C2) 98.07 (C3) 188.48 (C4) 136.03 (C5) 127.31 (C6) 155.35 (C7) 125.23 (C8) 160.95 (C9) 121.58 (C10) 114.59 (3-CN) 138.37 (C1') 129.44 (C2') 130.96 (C3') 170.33 (C4') 130.96 (C5') 129.44 (C6'). EIMS: *m/z* found 281.0248 (M$^+$). calcd for $C_{16}H_8NO_2Cl$: 281.0243 (M$^+$). Anal. Calcd for $C_{16}H_8NO_2Cl$: C, 77.72; H, 2.86; N, 4.97; Cl, 12.59. Found C, 77.81; H, 2.94; Cl, 12.63; N, 5.01.

3c : δ 7.85-7.90 (1H, dd, *J*=7.7 and 1.8 Hz, H-6), 7.50-7.60 (2H, d, *J*=8.2 Hz, H-2", 6"), 7.25 (1H, m, H-4), 7.15 (2H, d, *J*=8.2 Hz, H-3", 5"), 7.05 (1H, t, *J*=7.3 Hz, H-5), 6.60-6.80 (1H, d, *J*=8.1 Hz, H-3), 3.97-

3.98 (3H, s, OMe), 2.80-3.00 (2H, q, *J*=7.4 Hz), 2.30 (3H, s, Ar-Me), 1.20-1.40 (3H, t, *J*=7.4 Hz). δ^{13}C : 121.49 (C1) 153.69 (C2) 116.31 (C3) 134.03 (C4) 124.41 (C5) 129.91 (C6) 165.80 (C1') 93.43 (C2') 117.20 (2'-CN) 165.24 ($\underline{C}OOCH_3$) 52.60 ($COO\underline{C}H_3$) 27.41 ($S\underline{C}H_2CH_3$) 15.15 ($SCH_2\underline{C}H_3$) 131.46 (C1'') 128.99 (C2'') 129.50 (C3'') 21.16 (C4'') 129.50 (C5'')128.99 (C6'') 21.16 (4"CH_3). EIMS: *m/z* found 353.1072 (M^+). calcd for $C_{20}H_{19}NO_3S$: 353.1086 (M^+).

4c : δ 8.20 (1H, dd, *J*=8.0 and 1.7 Hz, H-5), 8.10 (2H, d, *J*=8.6 Hz, H-2', 6'), 7.80 (1H, d, *J*=7.9 Hz, H-7), 7.60 (2H, d, *J*=8.5 Hz, H-3', 5'), 7.50-7.60 (2H, m, H-6, 8), 2.30 (3H, s, Ar-Me). δ^{13}C : 172.03(C2) 97.86(C3) 174.95(C4) 127.83(C5) 125.88(C6) 136.56(C7) 119.76(C8) 155.99(C9) 122.73(C10) 115.56(3-CN) 128.17(C1') 129.69(C2') 130.46(C3') 144.88(C4') 130.46(C5') 129.69(C6') 22.12(C7'). EIMS: *m/z* found 261.07890 (M^+). calcd for $C_{17}H_{11}NO_2$: 261.0790 (M^+). Anal. Calcd for $C_{17}H_{11}NO_2$: C, 78.15; H, 4.24; N, 5.36. Found C, 77.12; H, 4.20; N, 5.64.

3d : δ 7.80-7.90 (1H, dd, *J*=7.8 and 1.8 Hz, H-6), 7.50-7.70 (2H, d, *J*=8.6 Hz, H-2", 6"), 7.25-7.40 (3H, m, H-5, 3", 5"), 7.05 (1H, t, *J*=7.6 Hz, H-4), 6.65-6.80 (1H, dd, *J*=8.3 and 1 Hz, H-3), 3.97-3.98 (3H, s, OMe), 2.8-3.00 (2H, q, *J*=7.4 Hz), 1.30-1.40 (3H, t, *J*=7.4 Hz), 1.26-1.28 (9H, s, *t*Bu). δ^{13}C : 124.13 (C1) 154.33 (C2) 119.04 (C3) 134.07 (C4) 125.39 (C5) 131.55 (C6) 164.25 (C1') 94.63 (C2') 121.18 (2'-CN) 165.13 ($\underline{C}OOCH_3$) 52.57 ($COO\underline{C}H_3$) 27.34 ($S\underline{C}H_2CH_3$) 15.13 ($SCH_2\underline{C}H_3$) 128.19 (C1'') 128.68 (C2'') 125.84 (C3'') 153.82 (C4'') 125.84 (C5'')128.68 (C6'') 34.89 (4"$\underline{C}(CH_3)_3$) 30.91 (4"$C(\underline{C}H_3)_3$). EIMS: *m/z* found 395.1570 (M^+). calcd for $C_{23}H_{25}NO_3S$: 395.1555 (M^+).

4d : δ 8.25 (1H, dd, *J*=8.1 and 1.7 Hz, H-5), 8.10 (2H, d, *J*=8.5 Hz, H-2', 6'), 7.90 (1H, t, *J*=8.1 Hz, H-7), 7.60 (2H, d, *J*=8.1 Hz, H-3', 5'),7.30-7.60 (2H, m, H-6, 8). 1.45 (9H, s, *t*Bu). δ^{13}C : 171.30 (C2) 97.21 (C3) 174.28 (C4) 127.18 (C5) 125.22 (C6) 135.92 (C7) 119.08 (C8) 156.84 (C9) 121.57 (C10) 114.91(3-CN) 127.55 (C1') 128.96 (C2') 126.14 (C3') 155.34 (C4') 126.14 (C5') 128.96 (C6') 35.24 (C7') 30.94 (C8'). EIMS: *m/z* found 303.1246 (M^+). calcd for $C_{20}H_{17}NO_2$: 303.1259 (M^+). Anal. Calcd for $C_{20}H_{17}NO_2$: C, 79.19; H, 5.65; N, 4.62. Found C, 79.22; H, 5.71; N, 4.70.

3e : δ 7.80-7.90 (1H, dd, *J*=7.8 and 1.7 Hz, H-6), 7.65-7.70 (2H, d, *J*=8.8 Hz, H-2", 6"), 7.25-7.35 (1H, m, H-4), 7.05 (1H, t, *J*=7.5 Hz, H-5), 6.85 (2H, d, *J*=8.8 Hz, H-3", 5"), 7.70-7.80 (1H, d, *J*=8 Hz, H-3), 3.97-3.98 (3H, s, OMe), 3.77 (3H, s, Ar-OMe), 2.82-3.00 (2H, q, *J*=7.4 Hz), 1.27-1.41 (3H, t, *J*=7.4 Hz). δ^{13}C : 123.01 (C1) 153.84 (C2) 119.71 (C3) 134.02 (C4) 124.26 (C5) 131.90 (C6) 161.49 (C1') 92.47 (C2') 121.39 (2'-CN) 165.21 ($\underline{C}OOCH_3$) 52.58 ($COO\underline{C}H_3$) 27.47 ($S\underline{C}H_2CH_3$) 15.12 ($SCH_2\underline{C}H_3$) 131.46 (C1'') 130.87 (C2'') 114.38 (C3'') 165.14 (C4'') 114.38 (C5'')130.87 (C6'') 55.55 (4"OCH_3). EIMS: *m/z* found 369.1031 (M^+). calcd for $C_{20}H_{19}NO_4S$: 369.1035 (M^+).

4e : 8.30 (1H , dd, *J*=8.1 and 1.6 Hz, H-5), 8.10 (2H, d, *J*=9 Hz, H-2', 6'), 7.90 (1H, d, *J*=7.8 Hz, H-7), 7.60 (1H, d, *J*=7.8 Hz, H-6), 7.10 (2H, d, *J*=9 Hz, H-3', 5') 7.00 (1H, d, *J*=1.8 Hz, H-8). EIMS: *m/z* found 277.0725 (M^+). δ^{13}C : 170.79 (C2) 96.11 (C3) 174.37 (C4) 127.06 (C5) 125.17 (C6) 135.81 (C7) 119.01

(C8) 155.24 (C9) 122.17 (C10) 115.20 (3-CN) 121.47 (C1’) 131.20 (C2’) 114.76 (C3’) 163.48(C4’) 114.76 (C5’) 131.20 (C6’) 55.99 (C7’). Calc for $C_{17}H_{11}NO_3$: 277.0739 (M^+). Anal. Calcd for $C_{17}H_{11}NO_3$: C, 73.64; H, 4.00; N, 5.05. Found C, 73.54; H, 3.89; N, 5.10.

3f : δ 7.80-7.90 (1H, dd, *J*=7.8 and 1.7 Hz, H-6), 7.32 (1H, t, *J*=8.3 Hz, H-4), 7.28 (1H, d, *J*=8.2 Hz, H-6”), 7.16 (1H, d, *J*=1.7 Hz, H-2”), 7.06 (1H, t, *J*=7.6 Hz, H-5), 6.74 (1H, d, *J*=8.2 Hz, H-5”), 6.69 (1H, d, *J*=8.3 Hz, H-3), 5.95 (2H, s, OCH_20), 3.96 (3H, s, CO_2Me), 2.94 (2H, q, *J*=7.3 Hz), 1.34 (3H, t, *J*=7.3 Hz). $\delta^{13}C$: 116.32 (C1) 153.72 (C2) 108.64 (C3) 124.46 (C4) 108.69 (C5) 134.04 (C6) 164.38 (C1’) 93.47 (C2’) 121.38 (2’-CN) 165.19 ($\underline{C}OOCH_3$) 52.61 ($COO\underline{C}H_3$) 27.45 ($S\underline{C}H_2CH_3$) 15.14 ($SCH_2\underline{C}H_3$) 124.53 (C1’’) 131.46 (C2’’) 124.34 (C3’’) 147.63 (C4’’) 149.87 (C5’’)119.60 (C6’’) 102.19 (OCH_2O). EIMS: *m/z* found 383.0810 (M^+). calcd for $C_{20}H_{17}NO_5S$: 383.0827 (M^+).

3g : δ 7.80 (1H, d, *J*=8.8 Hz), 7.60-7.70(2H, m), 7.40 (3H, m), 6.60 (1H, dd, *J*=8.8 and 2.4 Hz), 6.20-6.30 (1H, d, *J*=2.4 Hz), 4.10 (3H, s), 3.70 (3H, s), 2.90-3.00 (2H, q, *J*=7.3 Hz), 1.30-1.40 (3H, t, *J*=7.3 Hz). $\delta^{13}C$: 113.57 (C1) 163.58 (C2) 106.23 (C3) 164.46 (C4) 110.21 (C5) 133.34 (C6) 155.56 (C1’) 93.82 (C2’) 116.26 (2’-CN) 165.12 ($\underline{C}OOCH_3$) 52.22 ($COO\underline{CH}_3$) 27.42 ($S\underline{CH}_2CH_3$) 15.17 ($SCH_2\underline{CH}_3$) 56.02 ($4OCH_3$) 131.01 (C1’’) 128.87 (C2’’) 129.07 (C3’’) 131.31 (C4’’) 129.07 (C5’’) 128.87 (C6’’). EIMS: *m/z* found 369.1028 (M^+). calcd for $C_{20}H_{19}NO_4S$: 369.1035 (M^+).

4g : δ 8.15 (1H, d, *J*= 8.8 Hz, 1H-5), 8.00-8.10 (2H, m, H-2’, 6’), 7.55-7.75 (3H, m, H-3’,4’, 5’), 7.10 (1H, d, *J*=8.40 Hz, H-6), 7.00 (1H, d, *J*=2.1 Hz, H-8), 3.90 (3H, s, OCH_3). $\delta^{13}C$: 171.05 (C2) 97.67 (C3) 173.2 (C4) 133.39 (C5) 116.27 (C6) 165.12 (C7) 101.69 (C8) 157.27 (C9) 115.19 (C10) 114.82 (3-CN) 56.65 (7-OCH_3) 130.32 (C1’) 128.98 (C2’) 129.20 (C3’) 126.71 (C4’) 129.20 (C5’) 128.98 (C6’). EIMS: *m/z* found 277.0729 (M^+). calcd for $C_{17}H_{11}NO_3$: 277.0739 (M^+). Anal. Calcd for $C_{17}H_{11}NO_3$: C, 73.64; H, 4.00; N, 5.05. Found C, 73.71; H, 4.09; N, 5.15.

3h : δ 7.80-7.90 (1H, d, *J*=8.8 Hz), 7.65 (2H, d, *J*=8.6 Hz), 7.30 (2H, d, *J*=8.6 Hz), 6.65 (1H, dd, *J*=8.8 and 2.5 Hz), 6.20-6.30 (1H, d, *J*=2.5 Hz), 3.93-3.92 (3H, s), 3.73 (3H, s OMe), 2.80-3.10 (2H, q, *J*=7.4 Hz), 1.27-1.43 (3H, t, *J*=7.4 Hz). $\delta^{13}C$: 113.52 (C1) 163.48 (C2) 106.24 (C3) 163. 68 (C4) 110.34 (C5) 133.39 (C6) 155.41 (C1’) 94.75 (C2’) 115.96 (2’-CN) 164.42 ($\underline{C}OOCH_3$) 52.23 ($COO\underline{CH}_3$) 27.42 ($S\underline{C}H_2CH_3$) 15.17 ($SCH_2\underline{C}H_3$) 56.12 ($4OCH_3$) 129.87 (C1’’) 129.07 (C2’’) 130.89 (C3’’) 136.03 (C4’’) 130.89 (C5’’) 129.07 (C6’’). EIMS: *m/z* found 403.0652 (M^+). calcd for $C_{20}H_{18}NO_4ClS$: 403.0645 (M^+).

4h : δ 8.20 (1H, d, *J*=8.9 Hz, H-5), 8.05 (2H,d, *J*=8.2 Hz, H-2’, 6’), 7.60 (2H, d, *J*=8.2 Hz, H-3’, 5’), 7.10 (1H, dd, *J*=8.9 and 2.4 Hz, H-6), 7.00 (1H, d, *J*=2.3 Hz, H-8), 4.00 (3H, s, OMe). $\delta^{13}C$: 170.04 (C2) 98.26 (C3) 173.21 (C4) 127.03 (C5) 116.50 (C6) 165.52 (C7) 102.07 (C8) 157.49 (C9) 115.54 (C10) 114.73 (3-CN) 56.91 (7-OCH_3) 129.41 (C1’) 131.04 (C2’) 129.64 (C3’) 138.60 (C4’) 129.64 (C5’) 131.04 (C6’). EIMS: *m/z* found 311.0355 (M^+). calcd for $C_{17}H_{10}NO_3Cl$: 311.0349 (M^+). Anal. Calcd for $C_{17}H_{10}NO_3Cl$: C, 65.50; H, 3.23; N, 4.49; Cl, 11.37. Found C, 65.55; H, 3.31; Cl, 11.31; N, 4.53.

3i : δ 7.80-7.85 (1H, d, *J*=8.8 Hz), 7.57 (2H, d, *J*=8.2 Hz), 7.10 (2H, d, *J*=8.2 Hz), 6.55 (1H, dd, *J*=8.8 and 2.4 Hz), 6.20-6.30 (1H, d, *J*=2.4 Hz), 3.94-3.93 (3H, s), 3.70 (3H, s), 2.93-3.04 (2H, q, *J*=7.4 Hz), 2.31 (3H, s), 1.30- 1.43 (3H, t, *J*=7.4 Hz). δ^{13}C **:** 116.11 (C1) 164.84 (C2) 120.00 (C3) 165.05 (C4) 124.46 (C5) 131.48 (C6) 153.62 (C1’) 94.28 (C2’) 121.50 (2’-CN) 165.05 ($\underline{C}OOCH_3$) 52.85 ($COO\underline{CH}_3$) 27.39 ($S\underline{C}H_2CH_3$) 15.15 ($SCH_2\underline{C}H_3$) 52.85 (4OCH_3) 130.96 (C1’’) 128.90 (C2’’) 129.03 (C3’’) 134.01 (C4’’) 129.03 (C5’’) 128.90 (C6’’) 15.15 (4”CH_3). EIMS: *m/z* found 383.1185 (M^+). calcd for $C_{21}H_{21}NO_4S$: 383.1191 (M^+).

4i : δ 8.20 (1H, d, *J*=8.9 Hz, H-5), 8.05 (2H, d, *J*=8.2 Hz, H-2’, 6’), 7.40 (2H, d, *J*=8.2 Hz, H-3’, 5’), 7.10 (1H, d, *J*=9 and 2.4 Hz, H-6), 7.00 (1H, dd, *J*=2.3 Hz, H-8), 3.98 (3H, s, OMe), 2.50 (3H, s, Ar-H). δ^{13}C : 170.87 (C2) 96.93 (C3) 173.24 (C4) 144.11 (C5) 126.66 (C6) 165.06 (C7) 116.18 (C8) 157.16 (C9) 114.96 (C10) 115.12 (3-CN) 56.62 (7-OCH_3) 127.41 (C1’) 128.90 (C2’) 144.55 (C3’) 129.75 (C4’) 129.75 (C5’) 128.90 (C6’) 21.44 (C7’). EIMS: *m/z* found 291.0889 (M^+). calcd for $C_{18}H_{13}NO_3$: 291.0895 (M^+). Anal. Calcd for $C_{18}H_{13}NO_3$: C, 74.22; H, 4.50; N, 4.81. Found C, 74.36; H, 4.58; N, 4.92.

3j : δ 7.80-7.90 (1H, d, *J*=8.8 Hz), 7.50-7.65 (2H, d, *J*=8.3 Hz), 7.35 (2H, d, *J*=8.3 Hz), 6.57 (1H, dd, *J*=8.8 and 1.8 Hz), 6.20-6.30 (1H, d, *J*=2.4 Hz), 3.95-3.94 (3H, s), 3.71 (3H, s), 2.80-3.04 (2H, q, *J*=7.4 Hz), 1.30-1.40 (3H, t, *J*=7.4Hz), 1.27 (9H, s, *t*Bu). δ^{13}C **:** 113.24 (C1) 163.65(C2) 105.26 (C3) 164.36 (C4) 109.70 (C5) 133.54 (C6) 155.80 (C1’) 116.24 (2’-CN) 164.54 ($\underline{C}OOCH_3$) 52.10 ($COO\underline{C}H_3$) 27.39 ($S\underline{C}H_2CH_3$) 15.17 ($SCH_2\underline{C}H_3$) 56.06 (4OCH_3) 128.28 (C1’’) 128.72 (C2’’) 125.83 (C3’’) 154.32 (C4’’) 125.83 (C5’’) 128.72 (C6’’) 34.92 (4”$\underline{C}(CH_3)_3$) 30.95 (4”$C(\underline{C}H_3)_3$). EIMS: *m/z* found 425.1655 (M^+). calcd for $C_{24}H_{27}NO_4S$: 425.1661 (M^+).

4j : δ 8.17 (1H, d, *J*=8.8 Hz, H-5), 8.07 (2H, d, *J*=8.6 Hz, H-2’, 6’), 7.62 (2H, d, *J*=8.6 Hz, H-3’, 5’), 7.10 (1H, dd, *J*=8.8 Hz and 2.2 Hz, H-6), 6.97 (1H, d, *J*=2.2 Hz, H-8), 3.97 (3H, s, OMe), 1.40 (9H, *t*Bu). δ^{13}C **:** 170.89 (C2) 97.01 (C3) 173.26 (C4) 126.71 (C5) 116.15 (C6) 165.08 (C7) 101.66 (C8) 156.74 (C9) 115.16 (C10) 114.98 (3-CN) 56.62 (7-OCH_3) 127.50 (C1’) 128.86 (C2’) 126.09 (C3’) 157.19 (C4’) 126.09 (C5’) 128.86 (C6’) 35.23 (C7’) 30.94 (C8’). EIMS: *m/z* found 333.1363 (M^+). calcd for $C_{21}H_{19}NO_3$: 333.1365 (M^+). Anal. Calcd for $C_{21}H_{19}NO_3$: C, 75.66; H, 5.74; N, 4.20. Found C, 75.87; H, 5.74; N, 4.26.

3k : δ 7.80 (1H, d, *J*=8.8 Hz), 7.60 (2H, d, *J*=8.8 Hz), 7.80 (2H, d, *J*=8.8 Hz), 6.50 (1H, dd, *J*=8.8 and 2.3 Hz), 6.30-6.20 (1H, d, *J*=2.3 Hz), 3.90 (3H, s), 3.80 (3H, s), 3.70 (3H, s), 2.90-3.00 (2H, q, *J*=7.4 Hz), 1.40 (3H, t, *J*=7.4 Hz). δ^{13}C **:** 113.44 C1) 161.44 (C2) 105.88 (C3) 164.53 (C4) 109.92 (C5) 133.36 (C6) 155.80 (C1’) 92.28 (C2’) 116.68 (2’-CN) 165.37 ($\underline{C}OOCH_3$) 52.19 ($COO\underline{C}H_3$) 27.48 ($S\underline{C}H_2CH_3$) 15.14 ($SCH_2\underline{C}H_3$) 55.53 (4OCH_3) 123.07 (C1’’) 130.87 (C2’’) 114.34 (C3’’) 163.58 (C4’’) 114.34 (C5’’) 130.87 (C6’’) 56.05 (4”OCH_3). EIMS: *m/z* found 399.1134 (M^+). calcd for $C_{21}H_{21}NO_5S$: 399.1140 (M^+).

4k : δ 8.10-8.20 (1H, d, *J*=8.9 Hz, H-5), 8.20 (2H, d, J=9Hz, H-2’, 6’), 7.10 (2H, d, *J*=9 Hz, H-3’, 5’), 7.05 (1H, d, *J*=8.9 Hz, H-6), 7.00 (1H, d, *J*=2.3 Hz, H-8), 3.98 (3H, s, OMe), 3.96 (3H, s, Ar-OMe). $\delta^{13}C$ **:** 170.40 (C2) 95.89 (C3) 173.37 (C4) 126.64 (C5) 116.03 (C6) 165.00 (C7) 101.62 (C8) 157.08 (C9) 115.27 (C10) 115.05 (3-CN) 56.60 (7-OCH_3) 122.13 (C1') 131.07 (C2') 114.70 (C3') 163.38 (C4') 114.70 (C5') 131.07 (C6') 55.98 (C7'). EIMS: *m/z* found 307.0840 (M^+). calcd for $C_{18}H_{13}NO_4$: 307.0845 (M^+). Anal. Calcd for $C_{18}H_{13}NO_4$: 70.35; H, 4.26; N, 4.56. Found C, 70.31; H, 4.21; N, 4.61.

3l : δ 7.90 (1H, d, *J*=8.9 Hz), 7.30 (1H, d, *J*=8.8 Hz), 7.20 (1H, d, *J*=1.3 Hz), 6.8 (1H, d, *J*=8.8 Hz), 6.60 (1H, d, *J*=8.8 Hz), 6.20-6.30 (1H, d, *J*=2.3 Hz), 6.00 (2H, s), 4.00 (3H, s), 3.80 (3H, s), 2.80-3.00 (2H, q, *J*=7.4 Hz), 1.20-1.40 (3H, t, *J*=7.4 Hz). $\delta^{13}C$ **:** 113.41 (C1) 163.64 (C2) 105.78 (C3) 164.50 (C4) 108.69 (C5) 133.38 (C6) 155.69 (C1') 93.33 (C2') 116.42 (2'-CN) 164.60 ($\underline{C}OOCH_3$) 52.23($COO\underline{C}H_3$) 27.47 ($S\underline{C}H_2CH_3$) 17.17 ($SCH_2\underline{CH_3}$) 56.10 (4OCH_3) 124.59 (C1'') 108.69 (C2'') 124.44 (C3'') 147.61 (C4'') 149.83 (C5'')109.98 (C6'') 102.18 (OCH_2O). EIMS: *m/z* found 413.0925 (M^+). calcd for $C_{21}H_{19}NO_6S$: 413.0933 (M^+).

4l : δ 8.20 (1H, d, *J*=8.9 Hz, H-5), 7.80 (1H, dd, *J*=8.3 and 1.85 Hz, H-2'), 7.60 (1H, d, *J*=1.82 Hz, H-3'), 7.00-7.15 (3H, m, H-6, 8, 6'), 6.16 (2H, s, OCH_2O), 3.98 (3H, s OMe). $\delta^{13}C$ **:** 170.01 (C2) 96.09 (C3) 173.27 (C4) 126.59 (C5) 108.52 (C6) 165.03 (C7) 101.66 (C8) 157.03 (C9) 115.01 (C10) 115.10 (3-CN) 56.59 (7-OCH_3) 123.61 (C1') 108.90 (C2') 151.73 (C3') 148.03 (C4') 116.10 (C5') 125.02 (C6') 102.74 (C7'). EIMS: *m/z* found 321.0616 (M^+). calcd for $C_{18}H_{11}NO_5$: 321.0637 (M^+). Anal. Calcd for $C_{18}H_{11}NO_5$: 67.29; H, 3.45; N, 4.36. Found C, 67.32; H, 3.47; N, 4.43.

Bioassays

3-Cyanoflavones and their precursors were tested for bactericidal and fungicidal activities. The antimicrobial tests were performed *in vitro* using a liquid–phase turbidimetric system Bioscreen from Labsystem in honeycomb plates and automatically evaluated every 30 min for 24 h for the Bacteria and for 36 h for the fungi. The strains of Bacteria were *Escherichia coli* CIP 54 127, *Enterococcus hirae* CIP 58 55, *Staphylococcus aureus* CIP 53 154 (AFNOR : NF T 72-150). These were incubated in Mueller Hinton Broth at 37°C. The strains of fungi : *Candida albicans* CIP 1180-79 and *Saccharomyces cerevisiae* ATCC 28383 were incubated in Sabouraud Broth at 28°C. The tested molecules were dissolved in DMSO. In culture DMSO concentration never exceed 2%. The inocula (2%) were prepared from an overnight culture and diluted to obtain an absorbance (600 nm) of 0.5. Microorganisms were incubated under aseptic conditions in a shaker system and the growth curves were obtained by absorbance readings with wide band filter (420-580 nm). Antibacterial and antifungal activities were determined in terms of 50% inhibitory concentration (IC_{50}). The concentrations used were in the range of 0.8-100 µg mL^{-1}. As positive controls, penicillin G was used.

ACKNOWLEDGEMENTS

Authors would like to thank gratefully F. Pochat for helpfull discussion and P. Guenot for mass spectra.

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