Effects of Curcuminoid Pyrazoles on Cancer Cells and on the Expression of Telomerase Related Genes

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((Running head)) Effects of Curcuminoid Pyrazoles on Cancer Cell

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Graphical abstract(())

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R. Martí-Centelles, E. Falomir, M. Carda, C. I. Nieto, M. P. Cornago, and R. Claramunt**

A group of 13 curcuminoid pyrazoles were investigated for their cytotoxicity and their ability to downregulate the expression of the *h-TERT* and *c-Myc* genes, which are both involved in telomerase activity. (*E*)-3,5-Bis[β-(4-hydroxy-3-methoxyphenyl)-ethenyl]-1*H*-pyrazole (**1**) as the most active compound at 1 μM concentration reduces *hTERT* and *c-Myc* expression to 49% and 29%, respectively.

((Typesetter: please move the structure of Curcumin above that of the Curcumionoid pyrazoles))

Abstract

A group of 13 curcuminoid pyrazoles was investigated for their cytotoxicity on three tumoral cell lines (HT-29, MCF-7 and HeLa) and one non-tumoral human cell line (HEK-293). The values

obtained were compared with those of curcumin. A subset of selected derivatives was also studied for their ability to downregulate expression of the *hTERT* and *c-Myc* genes, which are both involved in telomerase activity.

Keywords: Combretastatin A-4 derivatives / Curcuminoid pyrazoles / Gene downregulation / Microtubules / Pironetin / Telomerase

Introduction

From time to time a new scaffold emerges in medicinal chemistry, and we feel that curcuminoid pyrazoles is one of them. If, as a scaffold, the pyrazole ring occupies the 44th position amongst the 100 most frequently used ring systems from small molecule drugs listed in the FDA [1] (34th considering only heterocycles), it has been considered important enough to devote a chapter to pyrazoles in the recent book "Privileged Scaffolds in Medicinal Chemistry: Design, Synthesis, Evaluation" [2]. The subset of curcuminoid pyrazoles start its appearance in 1991, when Flynn *et al.*, from the Parke-Davis Pharmaceutical Research Division of the Warner-Lambert Company, reported the 5-lipoxygenase and cyclooxygenase inhibitory properties of (*E*)-3,5-bis[β-(4-hydroxy-3-methoxyphenyl)-ethenyl]-1*H*-pyrazole (**1**) and related compounds **2**-**9** (Fig. 1) [3].

In a recent review [4] we reported 149 additional derivatives corresponding to 73 references for the years 2002-2015. Our past contribution to this field has consisted in four publications devoted to pyrazoles **1** and **10**-**21** (Fig. 2) as new therapeutic agents in inflammatory bowel disease [5], their annular tautomerism [6] and NOS inhibition [7]. We have also been active in the field of curcumin and the curcuminoids [8].
We wanted to know if such compounds **1**, **10-21** have other bio-pharmacological properties, and if these new properties are related to the previous ones. In particular, in the domain of cancer research, both curcumin and its derivatives [8d, 9] as well as pyrazole derivatives [10] have been reported to show interesting behavior.
The inhibitory effect of curcumin on gene expression is well-documented and reported in a large number of papers [11]. Human telomerase contains an RNA component (hTERC) that serves as a template for the addition of the repeated nucleotide sequences and a reverse transcriptase subunit (hTERT) which catalyzes the nucleotide polymerization process. Human telomerase is regulated during development and differentiation, mainly through transcriptional control of the *hTERT* gene, the expression of which is restricted to cells that exhibit telomerase activity. This indicates that the hTERT subunit is the rate limiting factor of the enzyme complex. It has been demonstrated that curcumin inhibits telomerase activity in a time- and dose-dependent manner by decreasing the level of *hTERT* gene expression thereby reducing proliferation of cancer cells [12].

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For the expression of the *hTERT* gene, several transcriptional factors such as c-Myc, a proto-oncoprotein [13], have been found to play an important role through upregulation of the mRNA encoding the hTERT protein subunit [14].

Thus, and as an initial study of the potential activity of our curcuminoid pyrazoles as inhibitors of telomerase activation, we have investigated their ability to inhibit tumor cell proliferation as well as their effect on hTERT and *c-Myc* gene expression.

Results and discussion

Chemistry

Compounds **1**, **10**-**21** were prepared by reaction of the corresponding β-diketones [8] with hydrazine hydrate 98% (Scheme 1), as already described by us in references 6 and 7.

Biological studies

Cytotoxicity of curcuminoid pyrazoles

We carried out a measurement of the cytotoxic activity of our synthetic curcuminoid pyrazoles [7] on three tumoral cell lines: the human colon HT-29, the breast adenocarcinoma MCF-7 and the cervix adenocarcinoma HeLa, as well as one non-tumoral cell line: the human embryonic kidney cell line HEK-293 [15]. Table 1 shows the cytotoxicity values for curcuminoids **1** and **10**-**21**, expressed as the compound concentration (μM) that causes 50% inhibition of cell growth (IC_{50}). Curcumin has been included for purposes of comparison. Table 1 further shows the α, β and γ coefficients, obtained by dividing the IC_{50} values of the normal cell line by those of either the HT-29, the MCF-7 or the HeLa cell line, respectively (see footnote in Table 1). The higher the value of either coefficient, the higher the therapeutic safety margin of the compound in the corresponding cell line.

The cytotoxicity of curcuminoid derivatives **1**, **10**-**21** is in the low micromolar range. As regards the HT-29 line, compounds **1**, **11** and **14** show IC_{50} values below that of curcumin. For MCF-7 cells, compounds **1**, **14** and **21** show IC_{50} values below that of curcumin and for HeLa cell line, compounds **1**, **14**, **15** and **21** show IC_{50} values below that of curcumin. Among these, compounds **1** and **14** are the ones that combine high cytotoxicity towards all studied tumoral cell lines.

Effect of selected curcuminoid pyrazoles on hTERT gene inhibition

In order to determine whether the curcuminoid pyrazoles were able to downregulate the expression of *hTERT* and c-Myc genes we have performed a reverse transcription quantitative PCR (RT-qPCR) analysis [16] using HeLa tumoral cells. For these measurements compounds **1**, **10**, **12**, **13**, **14**, **15**, **18**, **20** and **21** were selected because they exhibited reasonably good cytotoxicity towards HeLa cells (IC_{50} values below 30 μM). For these assays, concentrations

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lower than the IC_{50} values towards the HeLa cell line were used. Accordingly, concentrations were always 10 μM except for compound **1**, which was used at a concentration of 1 μM, and compound **21**, which was used at a concentration of 2 μM, because of their higher cytotoxicity on HeLa cells.

The expression of *hTERT* gene was determined by means of the RT-qPCR methodology, as described in the Experimental Section. Results for the selected compounds are depicted in Figure 3, which shows the percentage of *hTERT* gene expression after 48 h of incubation in the presence of DMSO (control experiment) and in the presence of each of the compounds investigated at a concentration of 10 μM (lower than their IC_{50} values) except 1 μM for **1** and 2 μM for **21**. All values were standardized (100%) to control (DMSO) and to β-actin.

Compounds **1** and **18** are able to significantly downregulate *hTERT* gene expression to 49% and 51%, respectively, a higher value than the one shown by curcumin (59%). The most remarkable compounds are **13** and **15**, which have the strongest inhibitory activity on the *hTERT* gene expression downregulating *hTERT* gene expression to 42% and 44%, respectively. Compounds **10**, **20** and **21** show no significant decrease in *hTERT* gene expression.

Effect of selected curcuminoid pyrazoles on c-Myc gene inhibition

In order to determine whether the studied compounds were able to regulate the expression of the *c-Myc* gene, we have performed a RT-qPCR analysis using again HeLa tumoral cells. The cells were incubated for 48 h in the presence of DMSO (control) and, as above, 10 μM of each of the studied compounds, except 1 μM for **1** and 2 μM for **21**. Results standardized (100%) to control (DMSO) and to β-actin are depicted in Figure 4.

Compounds **1, 13, 14** and **21** show the highest inhibitory effect on the expression of the *c-Myc* gene, downregulating *c-Myc* gene expression to 76%, 79%, 82% and 69%, respectively, a much greater inhibition than the one shown by curcumin, which inhibits 59% of the *hTERT* gene expression. Once again, compounds **10**, **20** and **21** show no significant decrease in *c-Myc* gene expression.

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Summary and Conclusions

The percentage of *hTERT* gene expression versus the percentage of *c-Myc* gene expression are graphically depicted in Figure 5. Compounds **1**, **13** and **15**, with relatively high inhibition levels on both biological targets *hTERT* and *c-Myc* gene expressions, are located in the lower left quadrant. This correlation between inhibition levels of *hTERT* and *c-Myc* gene expressions suggests that curcuminoid derivatives **1**, **13** and **15** are able to downregulate hTERT gene expression through downregulation of c-Myc transcription factor gene expression.

Compound **1**, at a concentration of 1 μM, and compounds **13** and **15**, both at 10 μM concentration, are able to decrease both gene expressions below fifty per cent. Moreover, these compounds features better than curcumin does at a concentration of 10 μM.

In summary, curcuminoid pyrazoles **1** and **10**-**21** have been evaluated for their biological activity against *hTERT* and *c-Myc* gene expressions. Though their cytotoxicities were in the low micromolar range, two of these derivatives, compounds **1** and **14,** exhibited lower IC_{50} values than curcumin towards all the studied cell lines. Moreover, compounds **1**, **14**, **15** and **21** exhibited lower IC_{50} values than curcumin towards HeLa cells. In this respect, they compare favorably with curcumin. All the selected compounds were more active than curcumin against both studied targets (Fig. 5). The most active compound was curcuminoid **1** because it was able to reduce the expression of the *hTERT* gene expression and it was also able of reducing to a large extent the expression of *c-Myc* gene. The curcuminoid pyrazoles **13** and **15** could be also considered very active compounds, as they were able to simultaneously reduce *hTERT* and *c-Myc* gene expressions (Fig. 6).

Correlation of the present results with those concerning our studies on the inhibitory activities of the same compounds against the three NOS isoforms is not obvious. As a whole our pyrazoles exhibited a major inhibition of the inducible iNOS isoform versus the constitutive isoforms nNOS and eNOS, those with fluorine atoms at positions 2' and 3' showing the higher inhibition percentages [7]. A statistical analysis of the inhibition percentages together with the selectivity coefficients α, β and γ (from this paper) for curcuminoids **1** and **10**-**21**, using a Free-Wilson matrix differentiating the fluorine atoms according to their position [7b], has shown that the six properties are independent. There is no relationship between cancer and NOS, nor between α, β and γ.

As regards curcumin itself it can be stated that the presence of the pyrazole moiety in the curcuminoid structures improves the studied biological properties. In addition, curcuminoid pyrazole derivatives **13**, **14** and **15**, which contain a trifluoromethyl group, perform better than pyrazoles **19**, **20** and **21** bearing a phenyl substituent. Of all the tested compounds, the best one is (*E*)-3,5-bis[β-(4-hydroxy-3-methoxyphenyl)-ethenyl]-1*H*-pyrazole (**1**), which formally derives from the replacement of the 1,3-dicarbonyl system of curcumin by a pyrazole ring.

Experimental

Chemicals

Curcumin is commercially available and was used after purification by crystallization from ethanol-water. (*E*)-3,5-bis[β-(4-hydroxy-3-methoxyphenyl)-ethenyl]-1*H*-pyrazole (**1**), (*E*)-3-[β-(2-fluoro-4-hydroxyphenyl)-ethenyl]-5-trifluoromethyl-1*H*-pyrazole (**10**), (*E*)-3-[β-(3-fluoro-4-hydroxyphenyl)-ethenyl]-5-trifluoromethyl-1*H*-pyrazole (**11**), (*E*)-3-[β-(2,4-difluoro-3-hydroxyphenyl)-ethenyl]-5-trifluoromethyl-1*H*-pyrazole (**12**), (*E*)-3-[β-(2,5-difluoro-4-hydroxyphenyl)-ethenyl]-5-trifluoromethyl-1*H*-pyrazole (**13**), (*E*)-3-[β-(4-fluoro-3-methoxyphenyl)-ethenyl]-5-trifluoromethyl-1*H*-pyrazole (**14**), (*E*)-3-[β-(4-hydroxy-3-methoxyphenyl)-ethenyl]-5-trifluoromethyl-1*H*-pyrazole (**15**), (*E*)-3-[β-(2-fluoro-4-hydroxyphenyl)-ethenyl]-5-phenyl-1*H*-pyrazole (**16**), (*E*)-3-[β-(3-fluoro-4-hydroxyphenyl)-ethenyl]-5-phenyl-1*H*-pyrazole (**17**), (*E*)-3-[β-(2,4-difluoro-3-hydroxyphenyl)-ethenyl]-5-phenyl-

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1*H*-pyrazole (**18**), (*E*)-3-[β-(2,5-difluoro-4-hydroxyphenyl)-ethenyl]-5-phenyl-1*H*-pyrazole (**19**), (*E*)-3-[β-(4-fluoro-3-methoxyphenyl)-ethenyl]-5-phenyl-1*H*-pyrazole (**20**) and (*E*)-3-[β-(4-hydroxy-3-methoxyphenyl)-ethenyl]-5-phenyl-1*H*-pyrazole (**21**) were crystallized from the appropriate solvent [6, 7] and their purity checked by thin layer chromatography and analytical techniques.

The InChI codes of the investigated compounds are provided as Supporting Information.

Biological procedures

Cell culture

Cell culture media were purchased from Gibco (Grand Island, NY, USA). Fetal bovine serum (FBS) was a product of Harlan-Seralab (Belton, U.K.). Supplements and other chemicals not listed in this section were obtained from Sigma Chemicals Co. (St. Louis, Mo., USA). Plastics for cell culture were supplied by Thermo Scientific™ BioLite. All tested compounds were dissolved in DMSO at a concentration of 10 μM and stored at –20°C until use.

Cell lines were maintained in Dulbecco's modified Eagle's medium (DMEM) containing glucose (1 g/L), glutamine (2 mM), penicillin (50 IU/mL), streptomycin (50 μg/mL) and amphoterycin (1.25 μg/mL), supplemented with 10% FBS.

RT-qPCR analysis

HeLa cells at 70–80% confluence were collected after serum starvation for 24 h. Cells were incubated with 10 μM of the corresponding drugs in DMSO for 48 h (for **1**, 1 μM and for **21**, 2 μM). Cells were collected and the total cellular RNA from HeLa cells was isolated using Ambion RNA extraction Kit according to the manufacturer's instructions. The cDNA was synthesized by MMLV-RT with 1-21 μg of extracted RNA and oligo(dT)15 according to the manufacturer's instructions.

Amplification of the genes was performed by use of a StepOnePlus™ thermalcycler. Fast TaqMan Gene Expression Master Mix containing the appropriate buffer for the amplification conditions, dNTPs, thermostable DNA polymerase enzyme and a passive reference probe was used. Each of the genes was amplified using predesigned primers by Life Technologies TaqMan® Gene Expression Assays, Hs99999903-m1 (β-actin), Hs00972646-m1 (hTERT) and Hs00153408-m1 (c-Myc).

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The authors have declared no conflict of interest.

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Figure 1. Derivatives with 5-lipooxygenase and cyclooxygenase inhibitory properties.

Figure 2. Curcuminoid pyrazoles synthesized and studied by our group.

Scheme 1. Synthetic scheme used to obtain pyrazoles **1**, **10**-**21** (for $R^{2'}$, $R^{3'}$, $R^{4'}$ and $R^{5'}$ see Fig. 2).

Figure 3. Expression percentage of the *hTERT* gene after 48 h of incubation of HeLa cells determined by means of the RT-qPCR methodology. At least three measurements were performed in each case. Concentration of all compounds was 10 μM except 1 μM for **1** and 2 μM for **21**. Error bars indicate standard errors of the mean. The statistical significance was evaluated using one-sample t-tests ($P < 0.001$).

Figure 4. Expression percentage of the *c-Myc* gene after 48 h of incubation of HeLa cells determined by means of the RT-qPCR methodology. At least three measurements were performed in each case. Concentration of all compounds was 10 μM, except 1 μM for **1** and 2 μM for **21**. Error bars indicate standard errors of the mean. The statistical significance was evaluated using one-sample t-tests ($P < 0.001$).

Figure 5. Percentage of *hTERT* gene expression vs. percentage of *c-Myc* gene expression.

Figure 6. Structures of three curcuminoid pyrazoles with potential multiple mode of action.

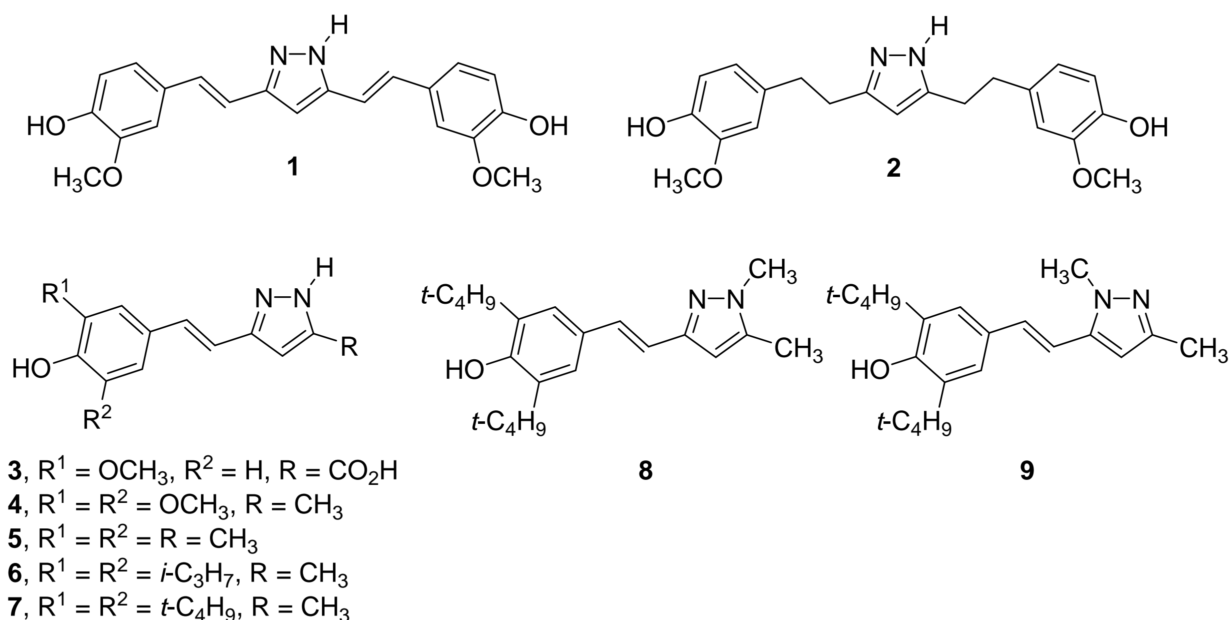

Figure 1

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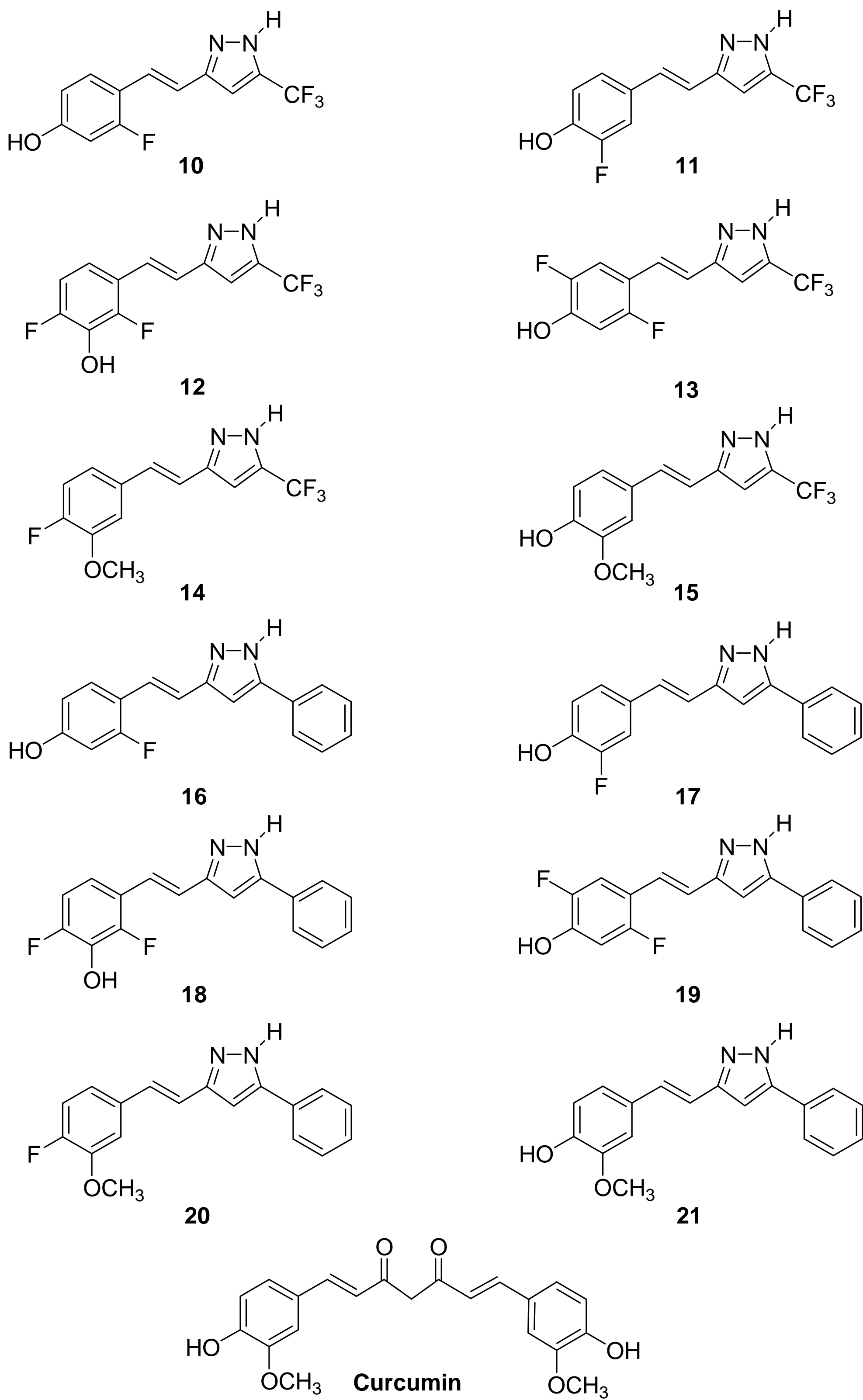
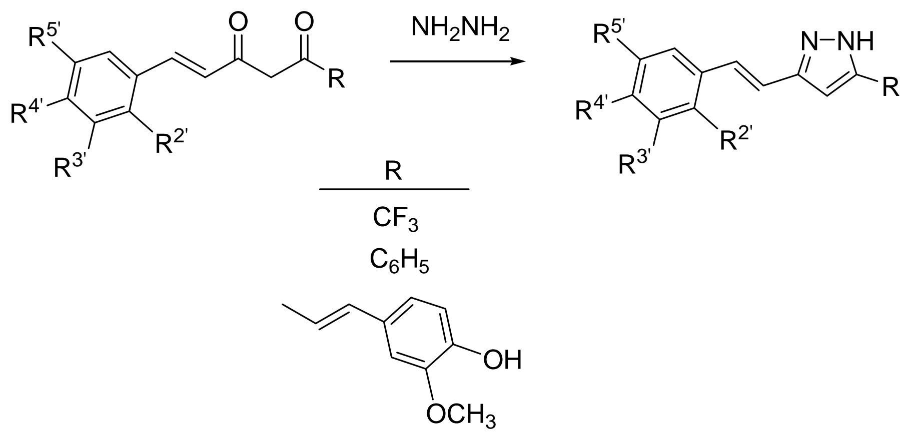


Figure 2



Scheme 1

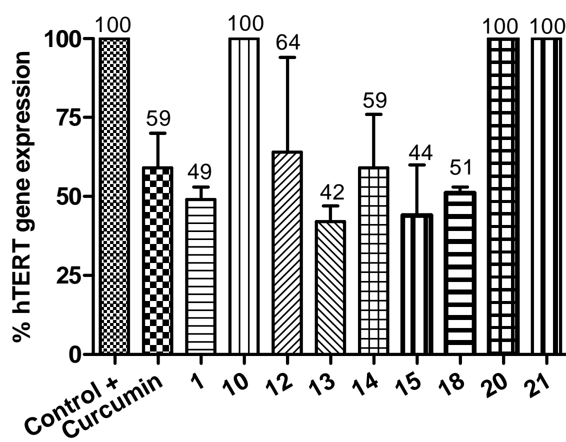


Figure 3

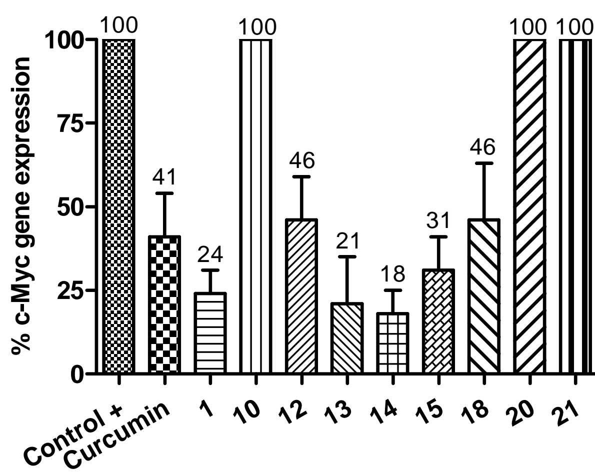


Figure 4

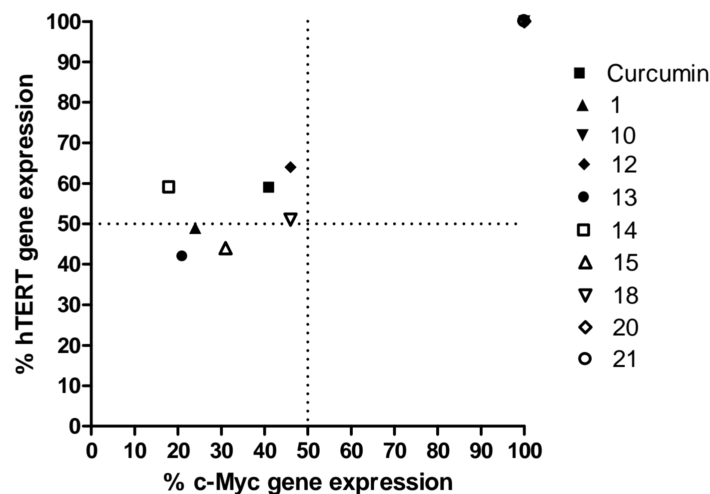


Figure 5

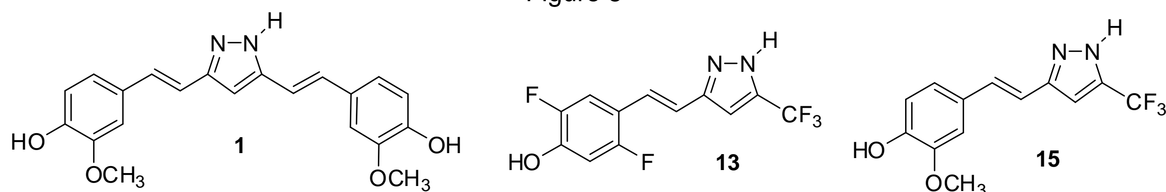


Figure 6

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Table 1. IC_{50} values (μM) and selectivity coefficients for curcuminoids 1 and 10-21.[a)]

Compd	HT-29	MCF-7	HeLa	HEK-293	α [b)]	β [c)]	γ [d)]
Curcumin	13.6 ± 2,5	18.3 ± 1,8	11 ± 4	10.8 ± 0,7	0.8	0.6	1.0
1	4.6 ± 1,4	11.1 ± 0,4	1.7 ± 0,6	0.72 ± 0.35	0.2	0.1	0.4
10	13.0 ± 2,2	32.2 ± 0,6	11.4 ± 0.3	26 ± 3	2.0	0.8	2.3
11	6.7 ± 0.4	90.6 ± 2.7	33 ± 5	48.2 ± 2.4	7.2	0.5	1.5
12	>100	>100	26 ± 3	50 ± 7	<0.5	<0.5	1.9
13	27.7 ± 2,6	87.5 ± 0,9	15.8 ± 1,8	13.69 ± 0.17	0.5	0.2	0.9
14	4.6 ± 1.0	13.7 ± 2.5	9.5 ± 2.2	2.9 ± 0.6	0.6	0.2	0.3
15	23.8 ± 2.7	75 ± 5	7.9 ± 2.9	31.0 ± 0.7	1.3	0.4	3.9
16	21.7 ± 4.4	27.2 ± 1.5	36.1 ± 3.4	32.6 ± 3.4	1.5	1.2	0.9
17	>100	>100	32 ± 3	53.1 ± 0,5	0.5	<0.5	1.7
18	33 ± 6	36.3 ± 1.1	16.0 ± 0.6	47 ± 5	1.4	1.3	2.9
19	39 ± 7	94.4 ± 2.4	34.82 ± 0.19	43 ± 9	1.1	0.5	1.2
20	19 ± 7	26 ± 6	18.0 ± 0.6	28 ± 5	1.5	1.1	1.6

21	22.4 ± 1.2	13.8 ± 1.4	3.8 ± 0.5	5.3 ± 1.9	0.2	0.4	1.4

[a] Values are the average (± s.d.) of three different measurements performed as described in the Experimental Section. [b] α = IC_{50} (HEK-293) / IC_{50} (HT-29). [c] β = IC_{50} (HEK-293) / IC_{50} (MCF-7). [d] γ = IC_{50} (HEK-293) / IC_{50} (HeLa). Values of α, β and γ have been rounded off to a decimal figure.

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