Curcumin derived pyrazoles and related compounds

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Pirazoles derivados de la curcumina y compuestos relacionados

Pirazoles derivats de curcumina i compostos relacionats

Rebut data: 11 de enero de 2016; aceptado: 14 de marzo de 2016

SUMMARY

In this comprehensive review we discuss the publications reporting pyrazoles derived from curcumin, curcuminoids and hemi-curcuminoids (149 examples) together with some biological and pharmacological properties.

Key words: Pyrazole; curcumin; curcuminoid; structure; biological properties.

RESUMEN

En esta revisión se discuten todas las publicaciones que tratan de pirazoles derivados de la curcumina, los curcuminoides y los hemi-curcuminoides (en total 149 ejemplos) así como algunas propiedades biológicas y farmacológicas.

Palabras clave: Pirazol; curcumina; curcuminoide; estructura; propiedades biológicas.

RESUM

En aquesta revisió es presenten les publicacions sobre pirazoles derivats de curcumina, curcuminoides i hemi-curcuminoides (149 exemples) així com algunes propietats biològiques i farmacològiques.

Paraulas clau: Pirazole; curcumina; curcuminoide; estructura; propietats biològiques.

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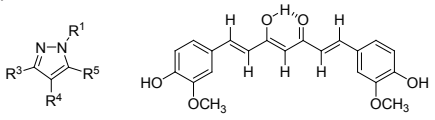
INTRODUCTION

We will limit our review to pyrazoles directly derived from curcumin or from other β-dicarbonyl compounds related to curcumin, i.e. possessing a styryl (save **2**, **16** and **133**) substituent bearing one or both OH and OCH_3 substituents. For general reviews concerning pyrazoles, see reference (1) and for reviews about curcumin see reference (2).



Curcuminoid pyrazoles have been discussed in some books (3), Master Degrees and Ph. D. Thesis (4), and have been the subject of several patents (5), but there is no comprehensive review about them. Excluding structures reported in patents, Figures 1 to 14 contain all the curcuminoid pyrazoles reported in the literature and Figures 15 to 17 those described in our publications. The first synthesis of the *N*-unsubstituted pyrazole derived from curcumin **1** was reported by Flynn et al., from the Parke-Davis Pharmaceutical Research Division of the Warner-Lambert Company, in 1991, and was tested as 5-lipoxygenase and cyclooxygenase inhibitor together with compound **2** (saturated branches) and the hemicurcuminoid pyrazoles **3**-**9** of Figure 1 (6).

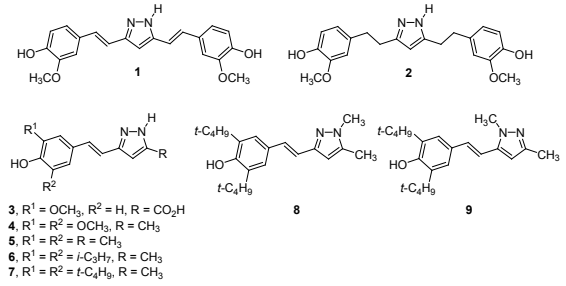


Figure 1. *The first series of pyrazoles* ***1-9*** *derived from curcumin and curcuminoids.*

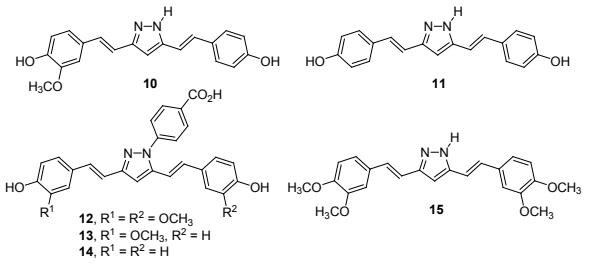


Figure 2*. Compounds* ***10-15.***

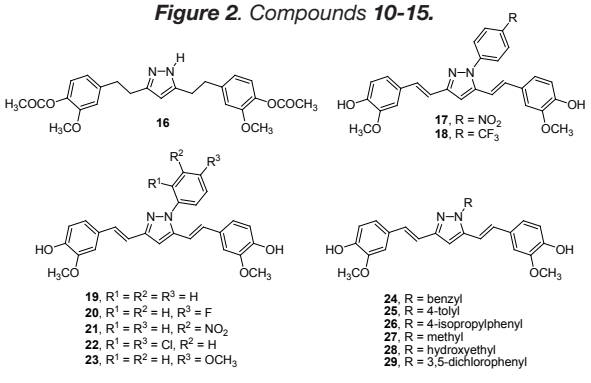


Figure 3. *Compounds* ***16-29****.*

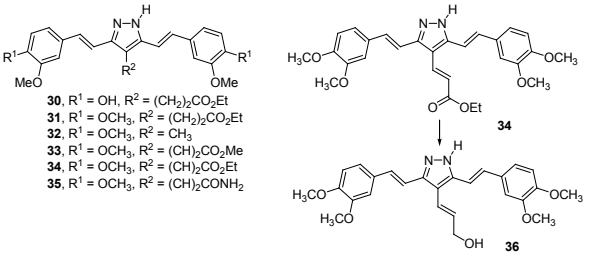


Figure 4. *Compounds* ***30-36****.*

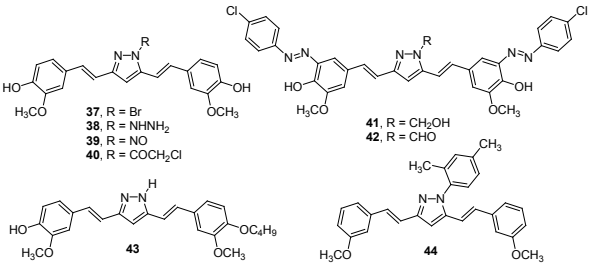


Figure 5. *Compounds* ***37-44****.*

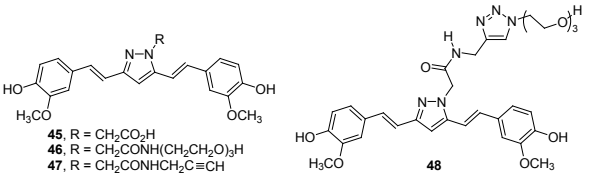


Figure 6. *Compounds* ***45-48****.*

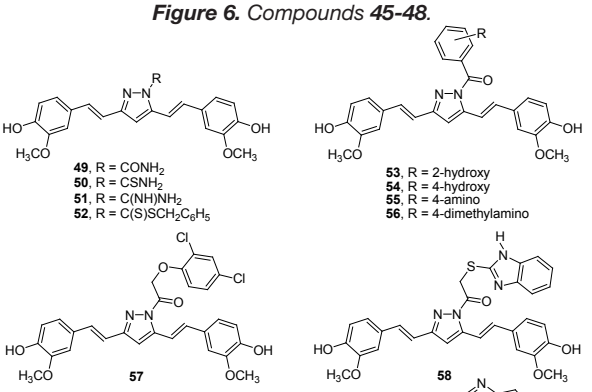
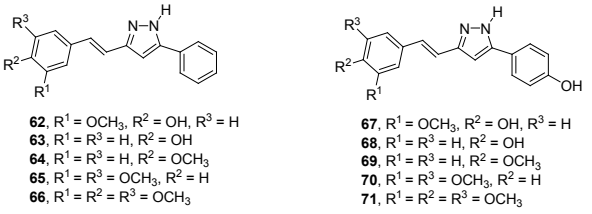
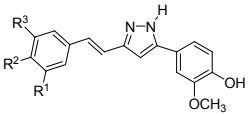


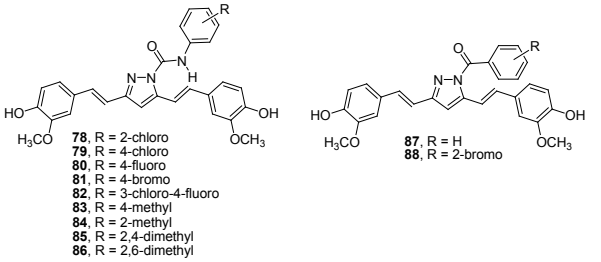
Figure 7. Compounds ***49-61***.





72, $R^1 = OCH_3$, $R^2 = OH$, $R^3 = H$
73, $R^1 = R^3 = H$, $R^2 = OH$
74, $R^1 = R^3 = H$, $R^2 = OCH_3$
75, $R^1 = R^3 = OCH_3$, $R^2 = H$
76, $R^1 = R^2 = R^3 = OCH_3$
77, $R^1 = OCH_3$, $R^2 = R^3 = H$

Figure 8. *Compounds* ***62-77****.*

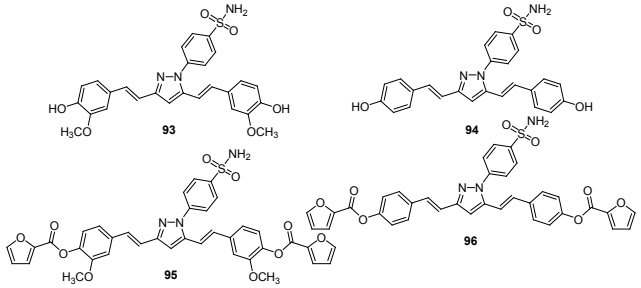


78, R = 2-chloro
79, R = 4-chloro
80, R = 4-fluoro
81, R = 4-bromo
82, R = 3-chloro-4-fluoro
83, R = 4-methyl
84, R = 2-methyl
85, R = 2,4-dimethyl
86, R = 2,6-dimethyl

87, R = H
88, R = 2-bromo

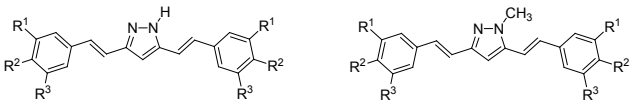
89 **90** **91** **92**

Figure 9. *Compounds* ***78-92****.*



93 **94** **95** **96**

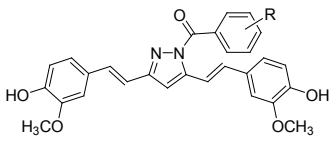
Figure 10. *Compounds* ***93-96****.*



97, $R^1 = R^3 = H$, $R^2 = OC_8H_{17}$
98, $R^1 = H$, $R^2 = OC_8H_{17}$, $R^3 = OCH_3$
99, $R^1 = H$, $R^2 = R^3 = OC_8H_{17}$
100, $R^1 = R^2 = R^3 = OC_8H_{17}$
101, $R^1 = R^3 = H$, $R^2 = OC^*H(CH_3)C_6H_{13}$

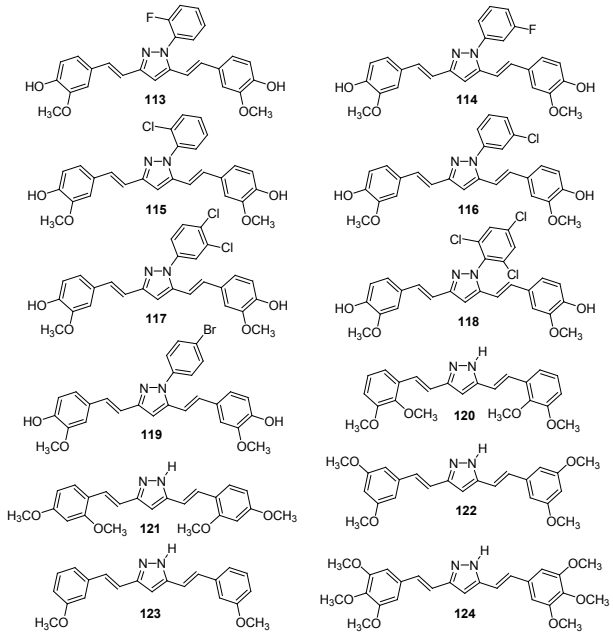
102, $R^1 = R^3 = H$, $R^2 = OC_8H_{17}$
103, $R^1 = H$, $R^2 = OC_8H_{17}$, $R^3 = OCH_3$
104, $R^1 = H$, $R^2 = R^3 = OC_8H_{17}$
105, $R^1 = R^2 = R^3 = OC_8H_{17}$

Figure 11. *Compounds* ***97-105****.*



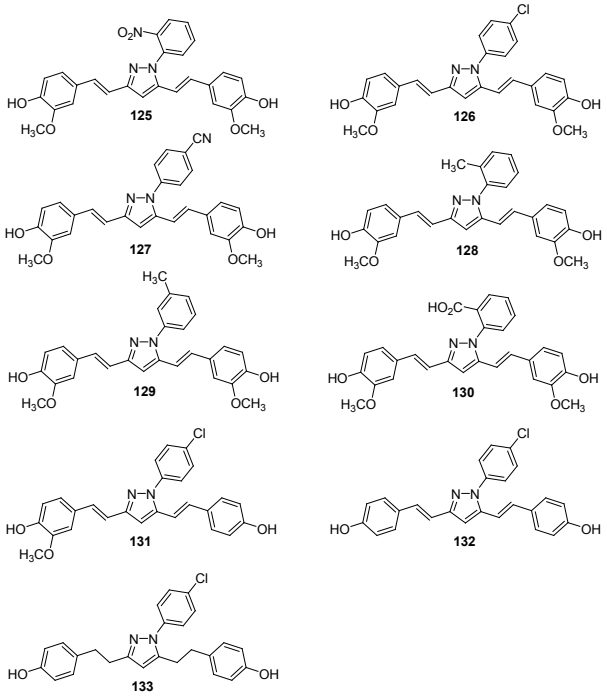
106, R = 2-chloro
107, R = 4-chloro
108, R = 4-methoxy
109, 4-pyridyl
110, 2-thienyl
111, benzyl
112, $CH_2OC_6H_5$

Figure 12. *Compounds* ***106-112****.*



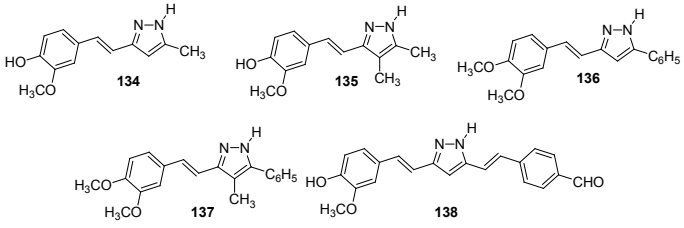
113 **114** **115** **116** **117** **118** **119** **120** **121** **122** **123** **124**

Figure 13. *Compounds* ***113-124****.*



125 **126** **127** **128** **129** **130** **131** **132** **133**

Figure 14. *Compounds* ***125-133****.*



134 **135** **136** **137** **138**

Figure 15. *Compounds* ***134-138****.*

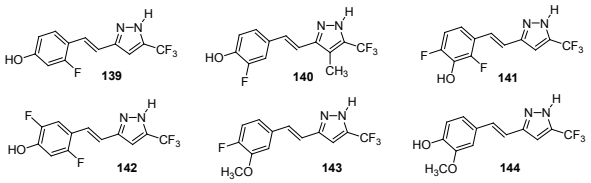


Figure 16. *Compounds* ***139-144****.*

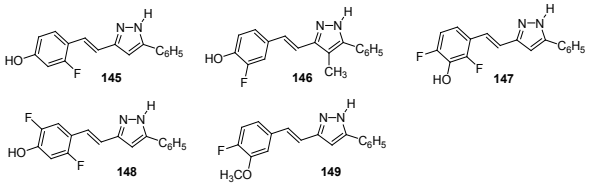


Figure 17. *Compounds* ***145-149****.*

We have prepared two tables to facilitate the search of any structure. Table 1 contains the references in chronological order (first, those from the literature, then, our publications) with the pyrazoles reported in them. Table 2 contains the 149 pyrazoles and the references where they are reported.

Table 1*. Publications ordered chronologically (from 6 to 64).*

Compounds	Ref.	Compounds	Ref.
1, **2**, **3**, **4**, **5**, **6**, **7**, **8**, **9**	(6)	**1**, **10**, **11**, **12**, **13**, **14**	(7)
1, **10**, **11**, **12**, **13**, **14**	(8)	**1**, **10**, **11**	(9)
1, **10**, **11**, **15**	(10)	**12**	(11)
1, **10**, **11**	(12)	**16**	(13)
12	(14)	**1**, **17**, **18**, **19**[CNB001],**20**,**24**, **25**, **26**	(15)
1, **19** [CNB001], **20**, **21**, **22**, **23**	(16)	**1**, **17**, **19** [CNB001], **21**, **24**, **25**, **26**, **27**, **28**, **29**	(17)
19 [CNB001]	(18)	**1**, **15**, **30**, **31**, **32**, **33**, **34**, **35**, **36**	(19)
1, **27**	(20)	**1**	(21)
1, **17**	(22)	**1**, **10**, **11**, **19** [CNB001]	(23)
12	(24)	**19** [CNB001]	(25)
1, **37**, **38**, **39**, **40**, **41**, **42**	(26)	**19** [CNB001]	(27)
1, 43	(28)	**19** [CNB001], **44** [CNB023]	(29)
28, **45**, **46**, **47**, **48**	(30)	**12**	(31)
19 [CNB001]	(32)	**49**, **50**, **51**, **52**, **53**, **54**, **55**, **56**, **57**, **58**, **59**, **60**, **61**	(33)
12	(34)	**1**	(35)
1	(36)	**1**	(37)
62, **63**, **64**, **65**, **66**, **67**, **68**, **69**, **70**, **71**, **72**, **73**, **74**, **75**, **76**, **77**	(38)	**78**, **79**, **80**, **81**, **82**, **83**, **84**, **85**, **86**, **87**, **88**	(39)
1, **12**, **27**, **32**, **33**, **34**, **43**	(40)	**19** [CNB001], **89**, **90**, **91**, **92**	(41)
19 [CNB001]	(42)	**1**, **12**, **28**	(43)
1, **11**, **93**, **94**, **95**, **96**	(44)	**19** [CNB001]	(45)
19 [CNB001]	(46)	**87**	(47)
19 [CNB001]	(48)	**97**, **98**, **99**, **100**, **101**, **102**, **103**, **104**, **105**	(49)
19 [CNB001]	(50)	**12**	(51)
49, **50, 55**, **78**, **79**, **80**, **81**, **84**, **87**, **88**, **106**, **107**, **108**, **109**, **110**, **111**, **112**	(52)	**1**, **19** [CNB001], **20**, **22**, **23**, **24**, **113**, **114**, **115**, **116**, **117**, **118**, **119**, **120**, **121**, **122**[Pculin02H], **123**, **124**	(53)
1, **17**, **19** [CNB001], **24**, **25**, **89**, **119**, **125**, **126**	(54)	**19** [CNB001], **23**, **89**, **116**, **127**	(55)
12	(56)	**12**	(57)
12	(58)	**1**, **19** [CNB001], **20**, **21**, **22**, **23**, **24**, **28**, **113**, **114**, **115**, **116**, **119**, **125**, **128**, **129**, **130**	(59)
126, **131**, **132**, **133**	(60)	**1**, **62**, **134**, **135**, **136**, **137**, **138**	(61)
1, **62**, **134**, **135**, **136**, **137**	(62)	**139**, **140**, **141**, **142**, **143**, **144**	(63)
145, **146**, **147**, **148**, **149**	(64)		

Table 2. *List of compounds from 1 to 149 with the figures where they are represented.*

Compound	References	Compound	References
1 (Figure 1)	(6,7,8,9,10,12,15,16,17, 19,20,21,22,23,26,28,35, 36,37,40,43,44,53,54,59, 61,62)	**2** (Figure 1)	(6)
3 (Figure 1)	(6)	**4** (Figure 1)	(6)
5 (Figure 1)	(6)	**6** (Figure 1)	(6)
7 (Figure 1)	(6)	**8** (Figure 1)	(6)
9 (Figure 1)	(6)	**10** (Figure 2)	(7,8,9,10,12,23)
11 (Figure 2)	(7,8,9,10,12,23,44)	**12** (Figure 2)	(7,8,11,14,24,31,34,40, 43,51,56,57,58)
13 (Figure 2)	(7,8)	**14** (Figure 2)	(7,8)
15 (Figure 2)	(10,19)	**16** (Figure 3)	(13)
17 (Figure 3)	(15,17,22,54)	**18** (Figure 3)	(15)
19 [CNB001] (Figure 3)	(15,16,17,18,23,25,27,29,32,41, 42,45,46,48,50,53, 54,55,59)	**20** (Figure 3)	(15,16,53,59)
21 (Figure 3)	(16,17,59)	**22** (Figure 3)	(16,53,59)
23 (Figure 3)	(16,53,55,59)	**24** (Figure 3)	(15,17,53,54,59)
25 (Figure 3)	(15,17,54)	**26** (Figure 3)	(15,17)
27 (Figure 3)	(17,20,40)	**28** (Figure 3)	(17,30,43,59)
29 (Figure 3)	(17)	**30** (Figure 4)	(19)
31 (Figure 4)	(19)	**32** (Figure 4)	(19,40)
33 (Figure 4)	(19,40)	**34** (Figure 4)	(19,40)
35 (Figure 4)	(19)	**36** (Figure 4)	(19)
37 (Figure 5)	(26)	**38** (Figure 5)	(26)
39 (Figure 5)	(26)	**40** (Figure 5)	(26)
41 (Figure 5)	(26)	**42** (Figure 5)	(26)
43 (Figure 5)	(28,40)	**44** [CNB023] (Figure 5)	(29)
45 (Figure 6)	(30)	**46** (Figure 6)	(30)
47 (Figure 6)	(30)	**48** (Figure 6)	(30)
49 (Figure 7)	(33,52)	**50** (Figure 7)	(33,52)
51 (Figure 7)	(33)	**52** (Figure 7)	(33)
53 (Figure 7)	(33)	**54** (Figure 7)	(33)
55 (Figure 7)	(33,52)	**56** (Figure 7)	(33)
57 (Figure 7)	(33)	**58** (Figure 7)	(33)
59 (Figure 7)	(33)	**60** (Figure 7)	(33)
61 (Figure 7)	(33)	**62** (Figure 8)	(38,61,62)
63 (Figure 8)	(38)	**64** (Figure 8)	(38)
65 (Figure 8)	(38)	**66** (Figure 8)	(38)
67 (Figure 8)	(38)	**68** (Figure 8)	(38)
69 (Figure 8)	(38)	**70** (Figure 8)	(38)
71 (Figure 8)	(38)	**72** (Figure 8)	(38)
73 (Figure 8)	(38)	**74** (Figure 8)	(38)
75 (Figure 8)	(38)	**76** (Figure 8)	(38)
77 (Figure 8)	(38)	**78** (Figure 9)	(39,52)
79 (Figure 9)	(39,52)	**80** (Figure 9)	(39,52)
81 (Figure 9)	(39,52)	**82** (Figure 9)	(39)
83 (Figure 9)	(39)	**84** (Figure 9)	(39,52)
85 (Figure 9)	(39)	**86** (Figure 9)	(39)
87 (Figure 9)	(39,47,52)	**88** (Figure 9)	(39,52)
89 (Figure 9)	(41,54,55)	**90** (Figure 9)	(41)
91 (Figure 9)	(41)	**92** (Figure 9)	(41)
93 (Figure 10)	(44)	**94** (Figure 10)	(44)
95 (Figure 10)	(44)	**96** (Figure 10)	(44)
97 (Figure 11)	(49)	**98** (Figure 11)	(49)
99 (Figure 11)	(49)	**100** (Figure 11)	(49)
101 (Figure 11)	(49)	**102** (Figure 11)	(49)
103 (Figure 11)	(49)	**104** (Figure 11)	(49)
105 (Figure 11)	(49)	**106** (Figure 12)	(52)
107 (Figure 12)	(52)	**108** (Figure 12)	(52)
109 (Figure 12)	(52)	**110** (Figure 12)	(52)
111 (Figure 12)	(52)	**112** (Figure 12)	(52)
113 (Figure 13)	(53,59)	**114** (Figure 13)	(53,59)
115 (Figure 13)	(53,59)	**116** (Figure 13)	(53,55,59)
117 (Figure 13)	(53)	**118** (Figure 13)	(53)
119 (Figure 13)	(53,54,59)	**120** (Figure 13)	(53)
121 (Figure 13)	(53)	**122** (Figure 13)	(53)
123 (Figure 13)	(53)	**124** (Figure 13)	(53)
125 (Figure 14)	(54,59)	**126** (Figure 14)	(54,60)
127 (Figure 14)	(55)	**128** (Figure 14)	(59)
128 (Figure 14)	(59)	**130** (Figure 14)	(59)
131 (Figure 14)	(60)	**132** (Figure 14)	(60)
133 (Figure 14)	(60)	**134** (Figure 15)	(61,62)
135 (Figure 15)	(61,62)	**136** (Figure 15)	(61,62)
137 (Figure 15)	(61,62)	**138** (Figure 15)	(61)
139 (Figure 16)	(63)	**140** (Figure 16)	(63)
141 (Figure 16)	(63)	**142** (Figure 16)	(63)
143 (Figure 16)	(63)	**144** (Figure 16)	(63)
145 (Figure 17)	(64)	**146** (Figure 17)	(64)
147 (Figure 17)	(64)	**148** (Figure 17)	(64)
149 (Figure 17)	(64)		

SYNTHESIS AND REACTIVITY

Many of these compounds were prepared by the classical method of reacting hydrazines with β-dicarbonyl compounds; since curcumin is "symmetrical" only one tautomer (R^1 = H) and one isomer ($R^1 \neq$ H) can be obtained. Others were obtained by reaction of pyrazoles at position 1, i.e. replacing the *N*-H proton by another group. In this way were obtained *N*-methyl, *N*-benzyl, *N*-CH_2CH_2OH, *N*-acyl, *N*-COR, etc. but not *N*-aryl derivatives. Some interesting transformations were reported; an example is the reduction of **34** by $NaBH_4$ to afford the

allylic alcohol **36** (19) and the synthesis of the elaborated compound **48** (30).
The name "hydrazinocurcumin" has been used for **1** and that of hydrazinobenzoylcurcumin for **12** (7), in both cases incorrectly.
It is suspected that the structure of the products reported in reference 26 may be wrong. For instance, the *N*-hydrazinopyrazole **38** was obtained from the *N*-bromo **37**, by reacting with hydrazine in ethanol, but this class of compounds is unknown. *N*-nitrosopyrazoles, like **39**, *N*-CH_2OH pyrazoles like **41** and *N*-formylpyrazoles like **42** are expected to be rather unstable.
The three most interesting compounds are **1**, **12** and **19** [CNB001] (**44** [CNB023] could become important in due time). If, from the chemical point of view, **1**, **19** and **44** are standard pyrazoles, pyrazole **12** has a weird history.
Compound **12** is 4-(3,5-bis((*E*)-4-hydroxy-3-methoxystyryl)-1*H*-pyrazol-1-yl) benzoic acid (often sold as its sodium benzoate). When described for the first time (7,8), it was called "Hydrazinobenzoylcurcumin", and other authors named it 4-{3,5-Bis-[2-(4-hydroxy-3-methoxy-phenyl)-ethyl]-**4,5-dihydro**-pyrazol-1-yl}-benzoic acid (HBC). The addition of the 4,5-dihydro term made it a 2-pyrazoline, and it was represented as such (11,31)! The compound has two code names HBC and CTK7A and it is commercially available as its sodium salt; again both suppliers (Merck Millipore, US Biological Life Sciences) made errors in the structural representation, the name and even the molecular formula; actually patents use the **4,5-dihydro**pyrazol-1-yl)benzoate wrong name (65). We hope that the present review will help to put things straight regarding compound **12**.

STRUCTURAL STUDIES

A large number of compounds are derivatives of curcumin itself, so when *N*-H (**1**) there are no problems of tautomerism and when *N*-R (**12**, **17**-**29**, **37**-**42**, **45**-**61**, **78**-**93**, **106**-**119**, **125**-**130**) there are no issues about isomerism. There are other pyrazoles where the substituents at positions 3 and 5 are identical (**2**, **11**, **14**-**16**, **30**-**36**, **44**, **94**-**96**, **97**-**101**, **102**-**105**, **120**-**124**) and therefore the same conclusions apply.
Pyrazoles have been considered as blocked tautomeric forms of the keto-enol of curcumin (66), but this idea, related to the aromaticity of the chelated enols of β-diketones (67,68), seems to us a little far-fetched. There are several cases where both tautomers are different (Figures 8, 15, 16, 17) but the only studies (NMR, crystallography, DFT calculations) on the tautomerism come from our group (61,62,63,64). It is possible that the fact that there is no clear relationship between tautomerism and biological activity explains the lack of studies about the tautomerism of pyrazoles related to curcumin in the literature. Since there are no examples of isomerism ($R^1 \neq H$ and $R^3 \neq R^5$), no spectroscopic studies have been carried out to determine the structure of the pyrazoles, i.e. which substituent is at position 3 and which at position 5.

BIOLOGICAL PROPERTIES

We will start discussing the idea, previously mentioned, that pyrazoles are isosteres of the enols of β-dicarbonyl compounds. The question is: "is this a rationale used for the design of curcuminoid pyrazoles?" or "is it an a posteriori rationalization'" when the pyrazoles, and particularly **1**, proved to be superior to curcumin? The first researcher that reported pyrazoles did not use this kind of argument in 1991 (6), and in 2002, the authors commented that "converting the keto-enol moiety to the corresponding pyrazole led to increased cytotoxicity against various cell lines", without any hypothesis about isosterism (9). It was not before 2007 that the argument that pyrazoles are isosteric with the enol of curcumin has been used (15,16,17,19,20, **26**,28,30,37,38,44,59,69).
Besides this reasoning, others were put forward to justify the good results obtained with pyrazoles (much better than with isoxazoles): i) the presence of an *N*–H group is necessary for its potency (a fact clearly not general considering compounds **12**, **19** and **44**) (16,19); ii) curcumin enol form was found to be responsible for its rapid degradation, degradation that can be prevented by transforming it into a pyrazole derivative (extremely stable at physiological pH) (37); iii) formation of pyrazole derivatives imposes a conformational constraint that is beneficial for activity, that is seemingly increased by rigidification (38); iv) curcumin-derived pyrazoles minimize the metal chelation properties of curcumin (17,44).
Concerning the relationships between biological properties and curcumin structure, the most elaborate contribution is that of Airoldi, La Ferla et al. (30) who carried out molecular mechanics (MM) and molecular dynamics (MD) to compare curcumin with compound **45** (Figure 6) (see Figure 18).

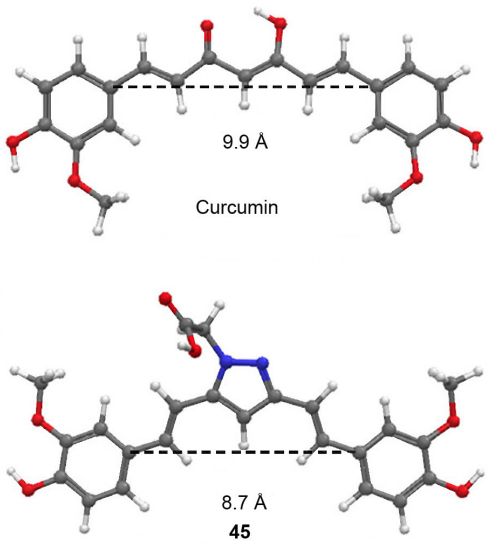


Figure 18. *Comparison of the geometries of curcumin and that of pyrazole* **45***, modified from reference 30.*

With the exception of one publication that dealt with curcuminoid pyrazoles compounds **97**-**105** as liquid crystals (Figure 11) (49), all the remaining articles report the pharmacological properties of curcuminoid pyrazoles. We have already published two reviews on the medicinal chemistry of pyrazoles (70,71), and we will discuss curcuminoid pyrazoles by pharmacological fields following the same order as in reference 70, omitting those that are empty, such as

antidepressants, antipsychotics, anxiolytics, sedatives and hypnotics. Being curcumin derivatives, it is normal that the most tested activities are related to those of curcumin itself: cancer, neurodegenerative diseases (Alzheimer, Parkinson), anti-inflammatory and anti-oxidant properties (72).

Anticonvulsants, analgesics, anti-Parkinson and anti-Alzheimer drugs

- Analgesics (36): Pyrazole **1** has a peripheral antinociceptive activity that is comparable to that of salicylates. This activity is related to its ability to inhibit COX and LO enzymes (6).
- Anti-Parkinson drugs: Jayaraj et al. reported in three papers (42,45,46) the therapeutic potential of **19** [CNB001] in the treatment of Parkinson disease. Curcuminoid pyrazoles, particularly **1** and **21**, inhibit deposition of the neurotoxic α-synuclein aggregates in the brain (59).
- Anti-Alzheimer drugs: Schmidt et al. (15,17) reported that curcuminoid pyrazoles inhibit the β-amyloid precursor protein metabolism, the most active compounds being **17** and **18**. Schubert's derivatives **19** [CNB001] and **44** [CNB023] were useful neurotrophic drugs for cognitive enhancement and treatment of Alzheimer's disease (AD) (29). Pyrazole **45** is a ligand of Aβ peptides and therefore useful for treating AD (30). The neuroprotective properties of **19** were reported by Schubert et al. (18). The same compound **19** [CNB001] restores membrane homeostasis disrupted after traumatic brain injury (TBI) (25), and it has been proposed to treat ischemic stroke (32,50).

Pharmacodynamic agents

- Antithrombotics. Compounds **1** and **11** show higher thrombin inhibition than **91** and **92** (44).

Agents acting on metabolic diseases and on endocrine functions

- Anti-inflammatory drugs and anti-arthritics: The parent compound **1** is a powerful 5-lipoxygenase (LO) and cyclooxygenase (COX) inhibitor (6); SAR studies revealed that replacement of the β–diketo fragment of curcumin by a pyrazole ring significantly enhances COX2/COX1 selectivity (compounds **1**, **10**, **11**) (12). Our personal contribution was aimed at the treatment of inflammatory bowel disease (IBD), Figure 15 (**62**, **134** -**138**) (61) and to the design of inhibitors of the different isoforms of the nitric oxide synthase (NOS) (**1, 62, 134-137, 139-149**) (63,64,73).
- Hypoglycemic, hypolipidemic and antiobesity agents. Treatment of obesity-associated insulin resistance by using **19** [CNB001] has been described (48). A study reporting the hypoglycemic properties of pyrazoles **19** and **116** has been published (55).

Chemotherapeutic agents

- Anticancer drugs: Kwon et al. published four papers on the antiproliferative properties of curcuminoid pyrazoles. The most interesting compounds are **1** and **12** (HBC or CTK7A). Compound **1** is an inhibitor of endothelial cell proliferation; **1** potently inhibited the proliferation of bovine aortic endothelial cells (BAECs) at nanomolar concentrations (IC_{50} = 520 nM) without cytotoxicity (7,8). Compound **12** in flexible docking models demonstrated that it is compatible with the binding cavity for a known inhibitor, W7, in the C-terminal hydrophobic pocket of Ca^{2+}/calmodulin (11). Its mechanism consists in inducing sustained phosphorylation of ERK1/2 and subsequently activating p21WAF1 expression in HCT15 cells. Moreover, **12** reversibly induced the G0/G1 cell cycle arrest in the cells (14). Finally, these authors showed that **12** inhibits the androgen receptor (AR) activity by targeting the AR amino-terminal domain and suggest potential usefulness of **12** for effective treatment of castration-resistant prostate cancer (CRPC) (58).

Lee et al. prepared and evaluated for in vitro cytotoxicity against a panel of human tumor cell lines four curcuminoid pyrazoles **1**, **10**, **11** and **15** (9,10). Compound **1** was active in all cell lines, whereas, compounds **10** and **11** exhibited selective activity against the 1A9 (breast cancer) cell line. However, as potential androgen receptor antagonists against two human prostate cancer cell lines, converting the β-diketone moiety to the corresponding pyrazole derivative greatly reduced the activity.

A series of pyrazoles, **1**, **15**, **30**-**36**, were evaluated against two breast cancer cell lines, which resulted in the identification of several compounds that exhibit anti-proliferative activity. These data were compared with their electrophilicity (1,4-conjugate addition of benzyl mercaptan, see also 21). The pyrazoles are more potent than the corresponding isoxazoles but less than curcumin and its derivatives. The most potent compound is **1** (MCF-7, IC_{50} = 4.2 μM) (19). Against prostate and breast cancer lines, pyrazole **1** (IC_{50} 5.4 μM in average) is three times more potent than its *N*-methyl derivative **27** (IC_{50} 16.1 μM in average) (20). The anti-tumor properties of **1** have been the subject of many studies (for a review, see reference 35): pro-apoptotic effects on liver cancer (21); cytotoxic effect on Ehrlich ascites cells (EAC) viability (26); free-radical scavenging activity and inhibition of the proliferation of A549 cells under serum-free conditions (37); tubulin-binding properties and anti-mitotic agents potentially selective for cancer cells (38); interaction with protein kinase-Cδ (PKC-δ), especially with the activator-binding second cysteine-rich C1B subdomain; compared with curcumin, pyrazole **1** exhibited increased cell growth inhibitory and pro-apoptotic effects in liver cancer HA22T/VGH cells as well as in other tumor cell types (40). Another much studied compound is **12** [CTK7A], especially by Zhou et al. (51,56,57) that have reported that it induces autophagy in A549 lung cancer cells through activating AMP-activated protein kinase (AMPK) signal (57). **12** [CTK7A] is an inhibitor of nitric oxide-mediated histone hyperacetylation in oral cancer (24).

Ahsan et al. evaluated the in vitro anticancer activity of eleven pyrazoles, **78**-**88**, on 60 cell lines (39,40). The most active is compound **87**, the 1-benzoylpyrazole derived from curcumin, which showed GI_{50} values between 0.008 and 1.9 μM in a 5-dose assay. **122** [Pculin02H] inhibits proliferation and clinical drug resistance of HER2-overexpressing cancer cells, being more effective than curcumin and other derivatives, even **19** [CNB001] (53). Our studies on the effects of curcuminoid pyrazoles **1**, **62** and **139**-**149** on cancer cells and on the expression of telomerase related genes were recently published (74).

Antibacterial and antiprotozoal

- Antibacterial: Pyrazoles **51**, **59** and **61** showed remarkable antibacterial activities (33). Pyrazoles **89**-**92** inhibit *S. aureus* with MIC between 0.06 and 0.25 mg/mL (41).
- Antimalarial: Pyrazoles **1**, **19**-**22** were tested as antimalarial agents: the most potent were **1** and **21** that can be considered a novel class of highly selective *P. falciparum* inhibitors (16). Pyrazoles **49**, **50**, **55**, **78**-**81**, **84**, **87**, **88**, **106**-**112** were prepared for possible PfRIO-2 kinase inhibitory action, an interesting approach to find anti-malarial compounds; the most active pyrazole being the *para*-fluoro derivative **80** (52).

It is clearly apparent that other fields should be explored since it is by no means evident that curcuminoid pyrazoles

must have the same biological properties as curcumin. They are not only "enhanced curcumins" but compounds with their own pharmacological profile

CONCLUSION

From our review it can be withdrawn that a large number of pyrazoles, isosteres of the curcumin enol form, have been synthesized from β-dicarbonyl compounds and hydrazine derivatives, proving to have interesting biological properties to fight cancer, neurodegenerative diseases, or inflammation and oxidation processes. Their activity is related to the conformational constraint arising from the heterocyclic ring and their potency to the presence of an *N*–H group. Contrary to curcumin, which is rapidly degradated at physiological pH, they are stable and minimize its metal chelation properties. It is expected that new pyrazole structures will be addressed in the future in which a fine tuning of the substitution pattern in the styryl branch will improve the pharmacological activities already found or discover new ones.

ACKNOWLEDGEMENTS

(Thanks are given to the Ministerio de Economía y Competitividad of Spain for financial support (Project numbers CTQ2012-13129-C02-02 and CTQ2014-56833-R) and Comunidad Autónoma de Madrid (S2013/MIT-2841, Fotocarbon). Computer, storage and other resources from the CTI (CSIC) are gratefully acknowledged. One of us (C. I. Nieto) is indebted to UNED for a predoctoral fellowship (FPI "Grupos de Investigación" UNED).

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