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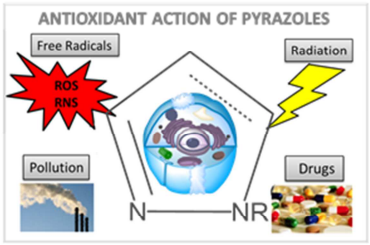

Current progress on antioxidants incorporating the pyrazole core

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Abstract

The search of new antioxidants, as drugs candidates, is an active field of medicinal chemistry. The synthesis of compounds with antioxidant potential has increased in recent years and a high number of structurally diverse compounds have been published. This review aims to show the current state-of-the-art on the development of antioxidant compounds incorporating the pyrazole pharmacophore. It is a well-timed review driven by the increasing number of papers, on this issue, that have been published since the beginning of the 21st century (from 2000-2017). The aim is to look deeper into the structures already published in the literature containing the pyrazole core as the unique pharmacophore or combined with other pharmacophores and see the relationship between the presence of this five-membered nitrogen heterocycle and the behaviour of the compounds as potential antioxidant agents. An attempt was made to whenever possible establish structure-activity relationships that could help the design of new and more potent antioxidant agents containing this important pharmacophore.

Keywords: Oxidative stress; Antioxidant; Free Radical; Nitrogen heterocycles; Pyrazole; Dihydropyrazole

Contents

Abbreviations

AA	Ascorbic acid
AAPH	2,20-Azobis(2-amidinopropane hydrochloride)
ABTS	2,20-Azinobis(3-ethylbenzothiazoline-6-sulphonic acid)
ADMET	Absorption distribution metabolism excretion and toxicity
AMG	Amtolmetin guacyl
AIP	Adiabatic ionization potential
AT1	Angiotensin II receptor type 1
BHA	2/3-(*Tert*-butyl)-4-methoxyphenol (Butylated hydroxyanisole)
BHT	2,6-di-*Tert*-butyl-4-methylphenol (Butylated hydroxytoluene)
CA	Caffeic acid
CAT	Catalases
CB1	Cannabinoid receptor type 1
DNA	Deoxyribonucleic acid
DPPH	1,1-Diphenyl-2-picrylhydrazyl
EC_{50}	Half maximal effective concentration
EDGs	Electron donating groups
EDTA	Ethylenediamine tetraacetic acid
EWGs	Electron withdrawing groups
FRAP	Ferric reducing antioxidant power
FRSA	Free radical scavenging activity
GA	Gallic acid

GPx	Glutathione peroxidase
GSH	Glutathione
HAT	Hydrogen atom transfer
HOMO	Highest occupied molecular orbital
IC_{50}	Half maximal inhibitory concentration
LDL	Low density lipoproteins
LUMO	Lowest unoccupied molecular orbital
NADPH	Nicotinamide adenine dinucleotide phosphate (reduced form)
NDGA	Nordihydroguaiaretic acid
PRAP	Phosphomolybdenum reducing antioxidant power
ORAC	Oxygen radical absorbance capacity
RNS	Reactive nitrogen species
ROCK	Rho kinase inhibitors
ROS	Reactive oxygen species
RSA	Radical scavenging activity
SAR	Structure-activity relationship
SCA	Sickle cell anaemia
SET	Single electron transfer
SODs	Superoxide dismutases
SPLET	Sequential proton loss electron transfer
TBHQ	2-(*Tert*-butyl)benzene-1,4-diol (*tert*-butylhydroquinone)
TEAC	Trolox-equivalent antioxidant activity
TRAP	Total radical trapping antioxidant potential
XO	Xanthine oxidase

1. Oxidative stress: brief introduction

Oxidative stress is one of the major causes of significant illnesses like cancer, aging, atherosclerosis, rheumatoid arthritis, cardiovascular and autoimmune diseases and neurodegenerative disorders such as Alzheimer's and Parkinson's diseases [1]. It is caused by the presence in the body of oxygen and nitrogen reactive species (ROS and RNS, respectively), like peroxides (H_2O_2), free radicals (chemical compounds which contain an unpaired electron spinning on the peripheral layer around the nucleus) such as hydroxyl radical ($^{\bullet}OH$), superoxide anion radical ($^{\bullet}O_2^-$), nitric oxide radical ($NO^{\bullet}$) and singlet oxygen, peroxynitrite, among others. These species are generated from excessive oxidative stress and normal metabolic activities. The body has regulating mechanisms for detoxification of free radicals, ROS and RNS species, such as superoxide dismutase (SOD), catalase (CAT) and glutathione peroxidase (GPx), to prevent it from high concentrations of these species, if not, damage of the normal cell structures, embedded proteins, lipids, carbohydrates and also of the nitrogen bases of nucleic acids can occur leading to mutations and to the above-mentioned illnesses.

Antioxidants are the molecules that prevent cellular damage caused by oxidation of other molecules. They play a vital role in the body defence mechanism by scavenging or regulating the generation and elimination of ROS and RNS. A good balance between ROS and RNS and antioxidants is necessary for proper physiological function. The intake of dietary antioxidants, either naturally occurring or synthetic ones, can enhance protection against free radicals and improve the quality of life by preventing from several diseases while contributing for substantial savings in the cost of health care delivery. Thus, the design and synthesis of new compounds capable of acting as strong antioxidants with high efficiency and low toxicity is a growing research area in the field of medicinal chemistry.

According to their mode of action, antioxidants can be classified in four main groups[1,2]:

i) Free radical scavengers;

ii) Chelators of metal ions involved in catalysing lipid oxidation;

iii) Lipooxygenase inactivators;

iv) Oxygen scavengers that react with oxygen in closed systems.

There are several and effective methods for screening the antioxidant activity of natural antioxidants, either as pure compounds or as plant extracts and of synthetic compounds either *in vitro* or *in vivo*. *In vitro* methods, are more commonly used and can be divided into two major groups: 1) Hydrogen atom transfer reactions like oxygen radical absorbance capacity (ORAC), total radical trapping antioxidant potential (TRAP) and β-carotene bleaching; 2) Electron transfer reactions like trolox equivalent antioxidant capacity (TEAC), ferric reducing antioxidant power (FRAP), 1,1-diphenyl-2-picrylhydrazyl radical ($DPPH^{\bullet}$), superoxide anion radical ($O_2^{\bullet-}$), hydroxyl radical ($^{\bullet}OH$), nitric oxide ($NO^{\bullet}$) radical scavenging assays and total phenol assay [2]. Two review articles have been published on *in vitro* evaluation of antioxidant activity [2,3] and more recently, in 2013, a third review was published compiling and discussing all the probable methods that are used for *in vitro* and also *in vivo* evaluation of antioxidant activity [4]; therefore this issue will not be covered in the present review. Nevertheless it is important to mention that the radical-scavenging ability is regarded as the basic property of an antioxidant and 1,1-diphenyl-2-picrylhydrazyl radical ($DPPH^{\bullet}$) scavenging method was found to be the most commonly used for the *in vitro* antioxidant activity evaluation while detection of lipid peroxide (LPO) was found as

mostly used *in vivo* antioxidant assay. In any case, the antioxidant activity should not be concluded based on a single antioxidant test model.

2. Biological activities of pyrazoles

The pyrazole (1*H*-pyrazole, **1**, Fig. 1) is an aromatic five-membered heterocyclic ring constituted by three carbons and two adjacent nitrogen atoms, located at 1-and 2-positions [5]. *N*-Unsubstituted pyrazoles may present three identical and non-separable tautomers, due to rapid interconversion in solution, and it is usually impossible to unequivocally assign the proton resonances of the pyrazole core in the proton-nuclear magnetic resonance (^{1}H NMR) spectra of these compounds. Three partially reduced forms may also exist: 1-pyrazolines **2**, 2-pyrazolines **3** and 3-pyrazolines **4** (Fig. 1) [5,6].

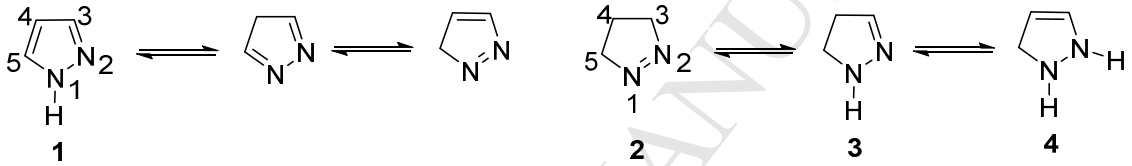


Fig. 1. Chemical structures and numbering of pyrazole and dihydropyrazole (pyrazoline) tautomers **1-4**.

The presence of the pyrazole scaffold or its reduced forms in natural compounds is rare, probably due to the difficulty of living organisms to construct N-N bond [7]. Nonetheless, pyrazole and its derivatives occupies a prime place in medicinal chemistry because it is present in many drugs with real medicinal application, such as celecoxib (Celebrex®) and sildenafil (Viagra®) and in several remarkable compounds with a wide range of pharmacological activities, namely antitumor, anti-inflammatory and antibacterial [8], antifungal, analgesic, antipyretic, antidepressant, antihypercholesterolemic, anticonvulsant, hypoglycemic, anticancer and cannabinoid activities [9,10,11,12,13,14,15,16]. The antioxidant activity of the pyrazole (1,2-diazole) **1** (Fig. 1) was revealed when it was used to treat nephrotoxicity caused by cisplatin. Cisplatin is an anti-neoplastic drug, used in the treatment of various cancers, but usually results in severe adverse effects namely nephrotoxicity or renal disorder through generation of ROS. Pre-treatment with pyrazole **1** was found to prevent nephrotoxicity induced by cisplatin through a protective mechanism that involved reduction of increased oxidative stress by significantly increasing the enzymatic and non-enzymatic antioxidant enzymes such as GPx, glutathione (GSH) and diminishing

the lipid peroxidation [17]. Along with the medicinal applications, pyrazoles are also useful as agrochemicals, such as herbicides, fungicides and insecticides [18] and possess other applications as dyestuffs, sunscreen materials [19] and as analytical reagents [20].

2.1. Antioxidants incorporating the pyrazole core

Regarding the study of the antioxidant activity of pyrazoles, results from our search in the Web of Science using the words "pyrazoles and antioxidants" highlighted that this is a recent and rising research topic with most of the papers being published in the last 10 years with a significant increase since 2013 (Fig. 2). Until 2008, only a few numbers of papers were published concerning the study of pyrazole as a pharmacophore with interest in the development of potential antioxidant compounds. However, since 2009, several compounds incorporating the pyrazole core or its reduced forms in their structures have been described as potential antioxidants. Also the number of citations of the papers published in this period has increased significantly in the last six years (Fig. 2), thus showing that this is an upward and important research topic.

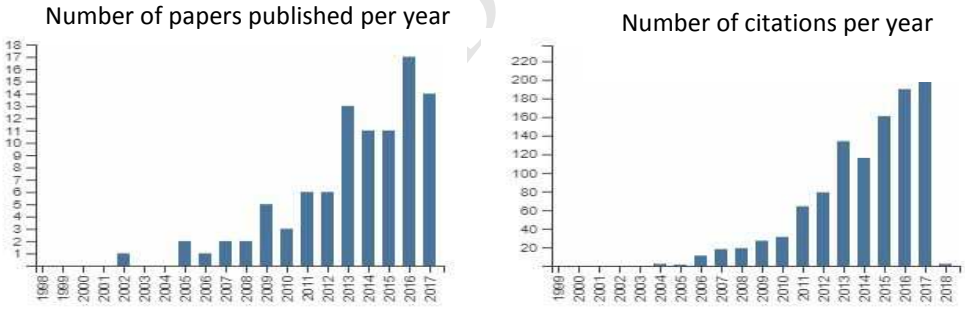


Fig. 2. Number of papers published and citations per year found using the keywords "pyrazoles and antioxidants" in Web of Science in the period 2000-2017.

This review is an attempt to compile the structures of pyrazole-derived compounds with antioxidant activity, published since the beginning of the 21st century, analyse the contribution of the pyrazole core for the antioxidant activity and, whenever possible, try to establish some structure-activity relationships. Some metal complexes of pyrazoles also have antioxidant activity; however, this type of compounds will not be included herein. To simplify, in the subtitles, the name pyrazole will be generally used, instead of

dihydropyrazole or (pyrazolines), when it refers to the reduced forms of pyrazole ring. In most of the studies published in this period, the antioxidant activity of the pyrazoles is compared with that of known antioxidants which are used as references. The structures of these standard compounds are represented in Fig. 3.

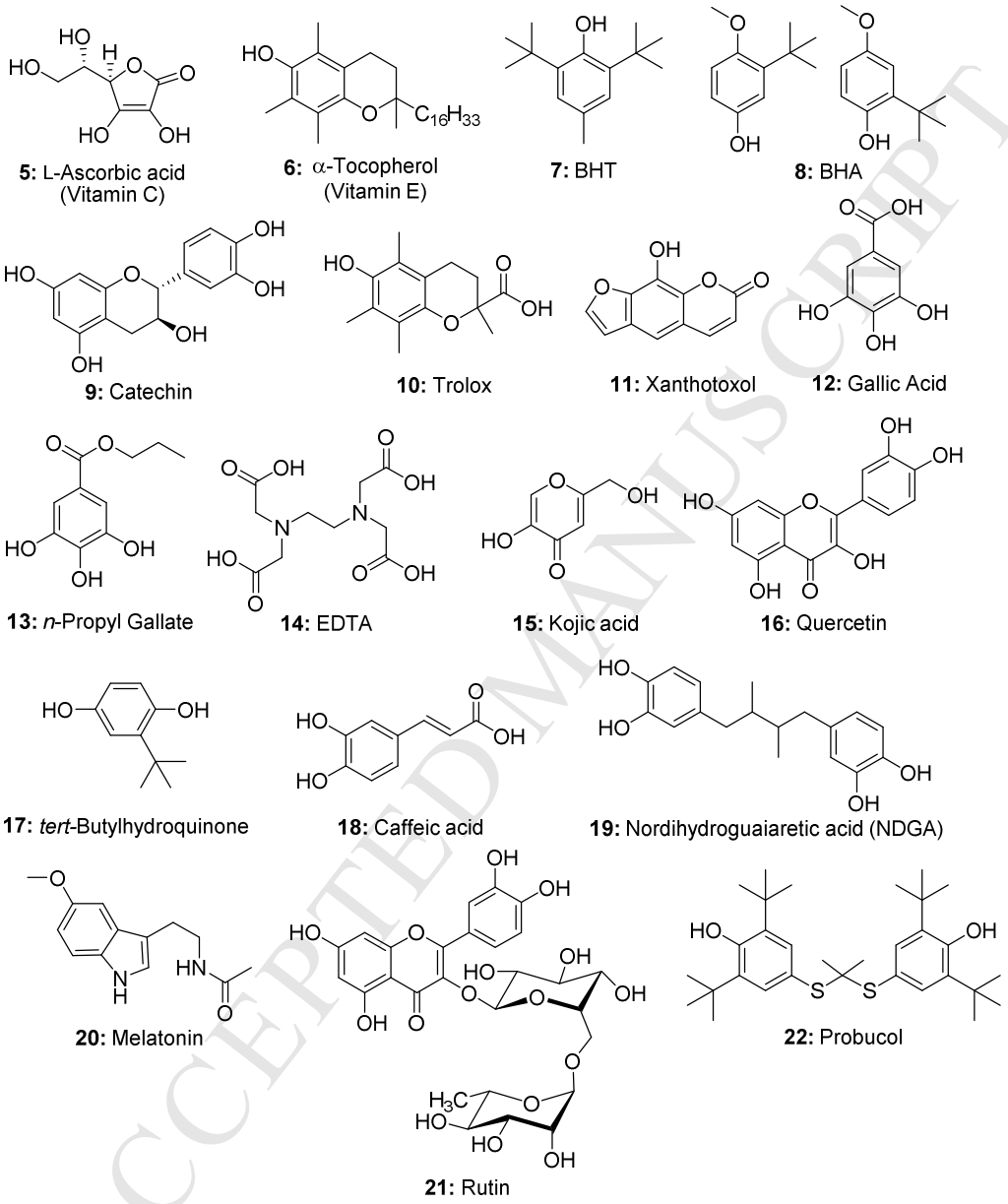


Fig. 3. Compounds used as standards in assays for assessment of the antioxidant activity.

2.1.1. 1,5-Diarylpyrazoles

1,5-Diarylpyrazoles **23a-h** (Fig. 4) exhibited moderate to excellent DPPH radical scavenging activity (RSA) (22.22 – 49.91% inhibition at 100 µg/mL) in comparison with the standard ascorbic acid (AA-**5**) (28.65 % inhibition at 100 µg/mL) [21]. Among these compounds, derivative **23b** also showed good anti-inflammatory activity. These results suggested that the presence of strong electron donating groups (EDGs) at *para*

position of the 5-phenyl ring is favourable to the anti-inflammatory activity while strong electron withdrawing groups (EWGs) decrease that activity. Molecular docking studies also suggested that compounds **23d** and **23b** possess better antioxidant and anti-inflammatory activities [21].

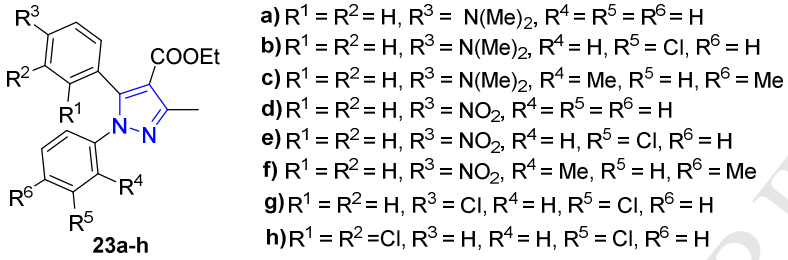


Fig. 4. 1,5-Diarylpyrazoles **23a-h** [21].

2.1.2. 3,5-Dialkyl/diarylpyrazoles

3,5-Dimethylpyrazole **24a-d** and 3-methylpyrazol-5-one **25a-d** derivatives of diclofenac, ibuprofen, flurbiprofen, 2,4-diclorophenoxy acetic acid and pyrazoline derivatives of ibuprofen **26a-e** (Fig. 5) were screened for their anti-inflammatory activity. Compounds **24a-c** and **26b** were the most active. In addition, compounds **24a-c** showed significant reduction of the ulcerogenic activity and of lipid peroxidation thus indicating good antioxidant activity which may be related with their anti-inflammatory and analgesic activities [22].

Various substituted pyrazolines **27a–j** and pyrazole **28** (Fig. 5) were examined *in vitro* for their abilities to protect human LDL against Cu^{2+}-induced peroxidation and compared with α-tocoferol **6** and probucol **22** [23]. Compound **27a** was the most active inhibitor of LDL oxidation being 6-fold more active than probucol **22** (0.6 μM), with IC_{50} values of 0.1 μM. The other substituted compounds **27c**,**e**, and **27g-j** were less effective than **27a** but more effective than probucol **22**. The conversion of compound **27a** into the oxidised derivative **28** led to a decrease of the LDL-antioxidant activity that becomes comparable to that of probucol **22**. It is clear that bulky di-*tert*-butyl groups contributed to more potent activity and that 2,6-di-*tert*-butylphenol is more reactive toward radical source to afford 2,6-di-*tert*-butylphenoxy radical in inhibition of free radical reaction. The presence of bulky groups suggests that steric and electronic factors of substituents to stabilize phenoxy radical formed from phenolic hydroxy group may influence antioxidant activities for human LDL.

The antioxidant activity of pyrazole **30** and pyrazolines **31a-f**, obtained by condensation of α,β-dibromo-4,4'-difluorochalcone **29** with hydrazine hydrate and various acid

hydrazides, was screened by DPPH assay (Fig. 5) [24]. When compared to the positive control, AA **5** (96.31 ± 0.34% DPPH radical scavenging), the tested compounds have demonstrated good to moderate RSA, ranging from 67.85 ±0.84 to 16.14 ±0.41, in the following decreasing order: **30** > **31c** > **31f** > **31a** > **31e** > **31b** > **29** > **31d**. Compound **30** was the most potent (67.85 ±0.84) probably due to the presence of acidic NH proton of pyrazole moiety. For compounds **31a-f** the variation in DPPH RSA could be attributed to the effect of different substitutions present in the compounds. With exception of **31d** (16.14 ±0.41) the less potent compound, all the tested compounds were more active than their precursor, the α,β-dibromo-4,4'-difluorochalcone **29** (20.46±0.12), thus indicating that the presence of the pyrazole ring strongly enhances RSA and consequently the antioxidant activity of these compounds.

A series of 3,5-diarylpyrazoline derivatives bearing a pyrimidine **32a-l** (Fig. 5) were screened for their FRSA by DPPH method [25]. At a concentration of 100 μg/mL pyrazolines **32b-d**,**i**,**j** exhibited excellent FRSA, 94.11, 93.51, 93.44, 89.79 and 90.51%, respectively. When compared to BHT **7** (93.16% at 100 μg/mL), pyrazolines **32b-d** showed higher activity than the standard, whereas the pyrazolines **32i**,**j** showed inhibition comparable to BHT **7**. Towards hydroxyl radical, pyrazolines **32b-d** presented the highest inhibition percentages, 89.12, 87.91, and 86.81 respectively, which are higher or similar than that of BHT **7** (86.98 % at 100μg/mL). Significant superoxide anion scavenging activity, comparable to that of BHT **7**, was shown by pyrazolines **32b-d**,**i**,**j**, as well as potent nitric oxide anion scavenging activity with exception of **32j**. Attempting on the substitution pattern of the most active pyrazolines, the presence of a halogen, Cl or Br, in one of the aromatic rings seems to be important for the antioxidant activity, while the presence of a strong EWG such as the nitro group is not beneficial, as well as the presence of halogens in both phenyl rings.

Other 1-substituted-3,5-diaryl-5-hydroxypyrazoline analogues **33a-l** (Fig. 5) have shown antioxidant activity when tested against DPPH$^{\bullet}$ radical [26]. The maximum RSA was found for compounds **33i**,**h**, followed by **33c** with IC_{50} values of 16.08, 16.61 and 17.70 μg/mL, respectively, which are comparable to those of the AA **5** (15.17 μg/mL) at 25 μg/mL. SAR studies revealed that EDGs, such as methoxy and methyl groups, are generally more beneficial than EWGs or unsubstituted groups in the phenyl rings.

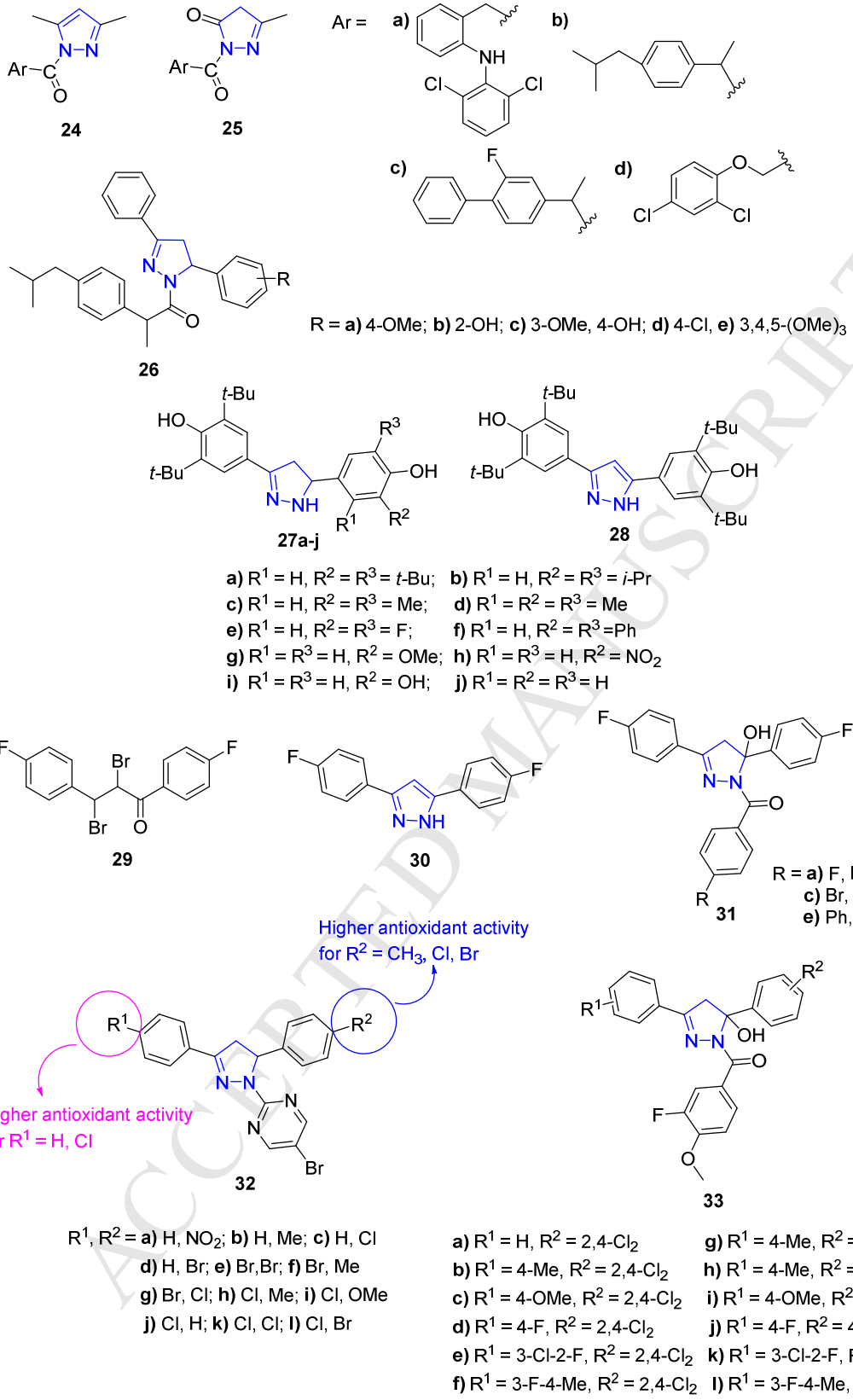


Fig. 5. 3,5-Dialkyl- and 3,5-diarylpyrazole derivatives **24-33** [22,23,24, 25,26**].**

2.1.3. 1,3,5-Triarylpyrazoles

Dendritic pyrazole-centred antioxidants in which pyrazole is the core having one phenolic and two phenyl groups at the periphery **34a-d** (Fig. 6) have shown similar ability to scavenge both $DPPH^{\bullet}$ and $ABTS^{+\bullet}$ radicals. Even pyrazole **34a** without a phenolic group has shown good RSA in ABTS and DPPH methods, indicating that the electron pair in the N atom of the pyrazole is able to trap radicals by donating its electron. On the other hand, the phenolic hydroxy group in pyrazoles **34b-d** does not exhibit stronger activity to trap radicals. This may be because the benzene ring in these pyrazoles does not completely form a conjugated system with the pyrazole ring, leading to the phenolic radical not being able to be stabilized by the whole conjugation system [27]. Only derivatives **34b** and **34c** have shown weak abilities to inhibit Cu^{2+}/GSH-induced oxidation of DNA, indicating that the hydroxy group originating from the chalcone precursor **35** rather than that from arylhydrazine plays a major role in the antioxidant action. However a pro-oxidant effect on $^{\bullet}OH$-induced oxidation of DNA was observed for these compounds, even for **34a**, which do not presents the phenolic hydroxy group. Nevertheless, the phenolic hydroxy group further increases the pro-oxidant effects. Pyrazole **34c** exhibited the highest ability to protect DNA against AAPH-induced oxidation, indicating that the hydroxy group at benzene ring B may enhance the antioxidant capacity in this case. Even though pyrazole **34a** also had a protective effect decreasing the oxidation rate of DNA, meaning that the N atom in pyrazole can also inhibit AAPH-induced DNA oxidation [27]. In comparison with *o*- and *p*-HBMC (Fig. 6), pyrazole derivatives **34a-d** have shown stronger antioxidant effectiveness in the inhibition of AAPH-induced DNA oxidation method, suggesting that the antioxidant effectiveness of these dendritic pyrazoles is superior to that of chroman-4-one, a classic structure found in natural antioxidants [27].

Eight ferrocenyl and three corresponding phenyl dendritic-like antioxidants containing dihydropyrazole or pyrazole as the core **36** (Fig. 6) exhibited RSA in the ABTS method and ability to protect DNA against AAPH-induced oxidation [28]. It was found that N atom in pyrazole is able to react with $ABTS^{+\bullet}$ radical but cannot react with peroxyl radical. Both hydroxy group and dihydro-structure are effective groups. The effect of hydroxy group is depending on its position in the molecule; It is greater when the hydroxy group is on the 5-phenyl and weaker when the hydroxy group is on the 3-phenyl of pyrazole ring. However, it is opposite for those derivatives with

dihydropyrazole as the core. For most dendritic-like antioxidants with dihydropyrazole or pyrazole as the core, antioxidant abilities, both in protecting DNA and ABTS RSA, are much greater if phenyl is replaced by ferrocenyl. This result exhibits the significant role of the ferrocenyl group. However, such role is also related to ferrocenyl position in the molecule. In $ABTS^{+\bullet}$ radical scavenging, the relationship between any two factors of ferrocenyl group, dihydrostructure, and hydroxyl group is synergetic but it is antagonistic when all of the three factors exist in the molecule together. In protecting DNA, the relationship between any two factors is synergetic only except what between hydroxy group and dihydrostructure is dubious. If all of the three factors exist in the molecule together, it will give out a highly synergetic result [28].

From the screening of the antioxidant activity of a series of 1,3,5-triaryl-2-pyrazolines **37a-g** (Fig. 6), compound **37a** (R = F) has shown good DPPH RSA, while the compounds **37c** (R = Br) and **37f** (R = OMe) have shown moderate DPPH scavenging activity, with concentration of 10 µg/mL in comparison with AA for all derivatives [29].

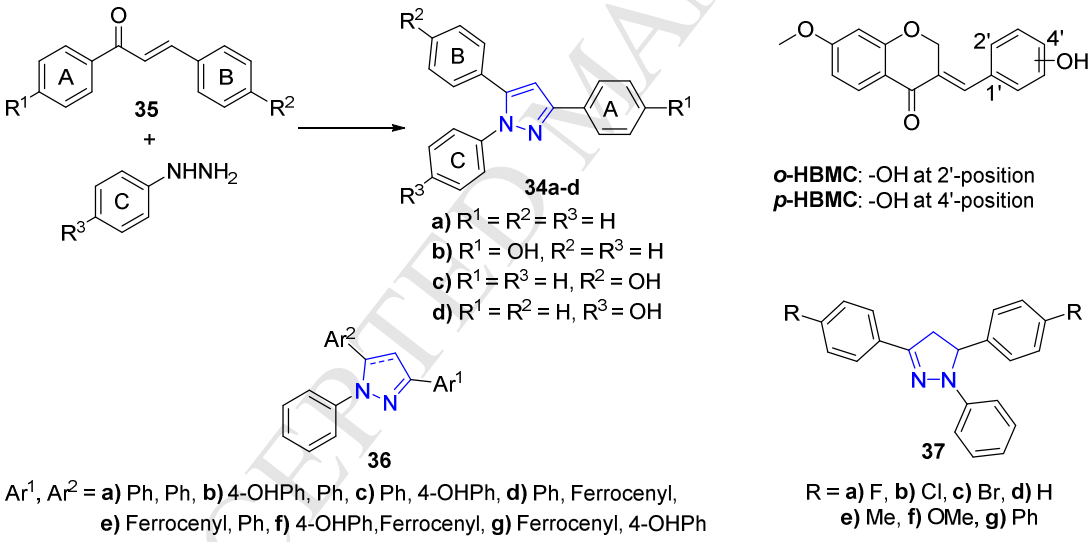


Fig. 6. 1,3,5-Triarylpyrazoles **34** and 1,3,5-triarylpyrazolines **37** [27,28,29].

2.1.4. Di/Triarylpyrazole-decorated nitriles

A series of 1-phenyl-4,5-dihydro-1*H*-pyrazole-5-carbonitriles **38a-h** (Fig. 7) showed promising DPPH RSA at concentrations 30-50 µg/mL but were less active than BHT **7**. Compounds **38a-d** were the most active showing RSA up to 60%, **38e,f,h** showed up to 45% and **38g** was the less active, 32%, with reference to BHT **7**. Strong EWGs enhanced the antioxidant activity while EDGs have the opposite effect. In addition, all compounds showed notable reducing power which was also higher in the case of compounds **38a-d**. The instability of the non-aromatic 1-phenyl-4,5-dihydro-1*H*-

pyrazole-5-carbonitriles **38a-d** explains the RSA of these compounds and the C4 and/or C5 positions of the pyrazoline ring may be the active site responsible for their antioxidant activity [30]. Other pyrazole-based nitriles **39a,b** (Fig. 7) have also shown antioxidant activity [31].

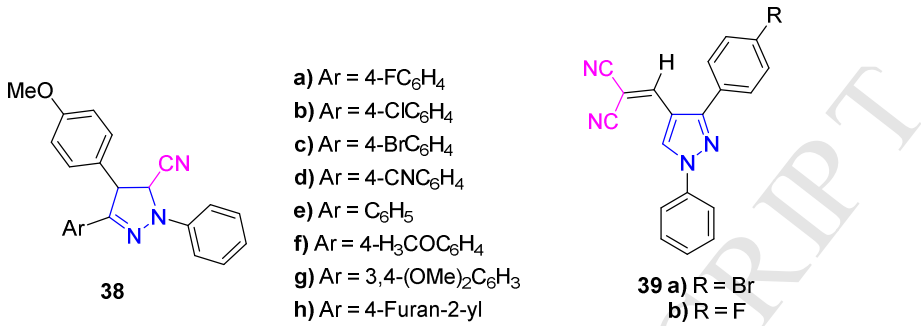


Fig. 7. Di- and triarylpyrazole-decorated nitriles **38** and **39** [30,31].

2.1.5. 3-Alkyl-5-hydroxy-5-trifluoromethylpyrazoles

From six novel pyrazolines **40a-f** (Fig. 8), 2-pyrazoline **40e** presented the highest FRSA in DPPH assay, higher than trolox **10**, and 2-pyrazoline **40b** had the highest FRAP value ($P < 0.05$), but lower than trolox **10** [32]. The protective effect against brain lipid peroxidation of these pyrazolines was different depending on the agent used to induce lipid peroxidation. Only pyrazolines **40a**,**d**,**e** demonstrated protective effects against lipid peroxidation in rat brain homogenates, however compound **40e** presented the greatest potential to prevent oxidative damage in brain homogenates. This compound was the most effective in the prevention of basal and iron-, sodium nitroprusside- and H_2O_2-induced lipid peroxidation ($IC_{50} < 15\mu M$) and was the only one effective to block GSH oxidation-mediated by H_2O_2 (at 150µM). Accordingly, compound **40e** was the most effective in all the conditions tested indicating that the presence of the hydroxybenzoyl group linked to the nitrogen of the pyrazole increases the antioxidant activity. Probably this group is involved in transferring labile electrons to the DPPH$^{\bullet}$ radical. The similar IC_{50} values of compounds **40a**,**d**,**e** against iron- and sodium nitroprusside-induced lipid peroxidation indicates that the basic structure of the pyrazole compounds has an important antioxidant activity [32].

Amongst a series of eight 5-hydroxy-5-trifluoromethyl-4,5-dihydro-1*H*-pyrazole-1-carboxamides **41a-h** (Fig. 8), those showing the highest antipyretic activity, **41c**,**d**, have shown DPPH RSA with IC_{50} values of 39 mM and 163 mM, respectively being only slightly active when compared to AA **5** whose IC_{50} was 0.024 mM [33]. Even so, the

authors suggested that the antipyretic activity of these compounds may be related to their antioxidant activity.

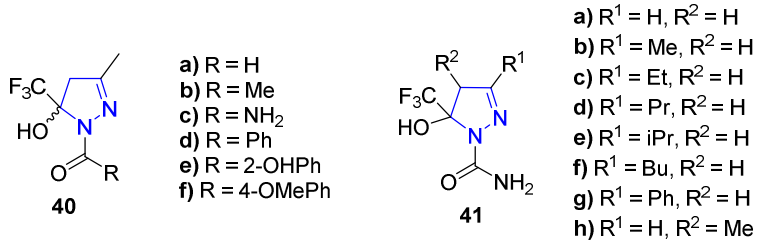


Fig. 8. 3-Alkyl/aryl-5-hydroxy-5-trifluoromethylpyrazole derivatives **40** and **41** [32,33].

2.1.6. 3,5-Diaminopyrazoles

Diaminopyrazoles **42c** and **43a** (Fig. 9) exhibited high antioxidant activity in both nitric oxide and DPPH methods at 100 µM concentration. The compounds bearing sulfone groups displayed more pronounced antioxidant activity than those with diaroyl groups and the maximum activity was observed with compounds having chloro substituent in the aryl moiety [34].

The tris-heterocycles **44-46** (Fig. 9) were tested for antioxidant activity by DPPH, nitric oxide and ABTS methods and compared with AA **5**. Compound **44** showed good RSA while compound **45** showed moderate activity and compound **46** was inactive. These results indicate that the compound with the benzoxazolyl moiety exhibits greater activity than those having benzothiazolyl or benzoimidazolyl units. Moreover, the combination of the benzoxazolyl with an isoxazole instead of pyrazole increases the antioxidant activity [35].

3,5-Diaminopyrazole **47** (Fig. 9) has shown potent antioxidant and analgesic activity, better than caffeine, and was indicated as a possible scaffold for development of new strong antioxidant and analgesic drugs with an effect on memory capacity. The IC_{50} of this compound was found to be 0.8 mg/mL. The 100% antioxidant activity was obtained for a concentration of about 2 mg/mL whereas the same dose of caffeine had no antioxidant effect [36].

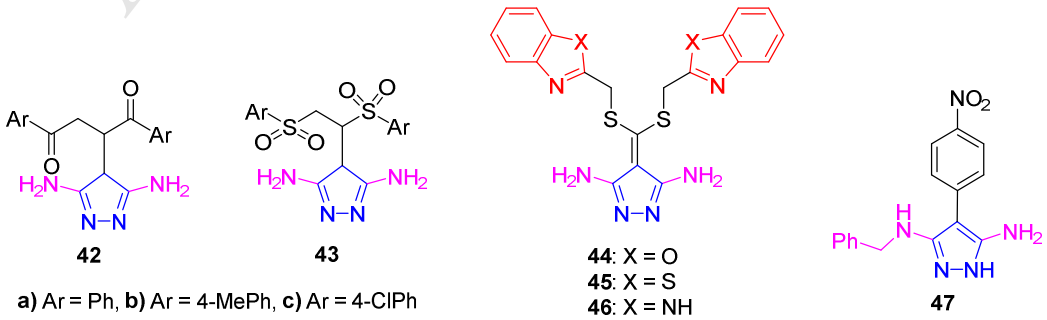


Fig. 9. 3,5-Diamino-4-substitutedpyrazoles **42-47** [34,35,36].

2.1.7. Celecoxib and other (pyrazol-1-yl)benzenesulfonamide related compounds

Several studies have shown additional antioxidant activity of celecoxib **48** (Fig. 10) beside its important analgesic, anti-inflammatory and anti-mutagenic activities [37,38]. Celecoxib has shown *in vitro* antioxidant activity by inhibition of lipid peroxidation in a concentration-dependent manner, with IC_{50} = 1.99 ± 0.05 μmol/mL, lower than that of the standard catechin **9** (1.44±0.09 μmol/mL) and by hydroxyl scavenging activity (IC_{50} = 1.97 ± 0.06 μmol/mL) being this effect higher than that of catechin **9** (2.93± 0.07 μmol/mL) [38]. While the exact mechanism by which celecoxib inhibits radical generation is unknown, the inhibition of lipid peroxidation may be due to direct scavenging of the peroxyl radical or by donating reducing equivalents to the peroxyl radical. A study published in 2007 has confirmed the ability of celecoxib to affect some indices of the oxidative stress, such as lipid peroxidation activity of antioxidant enzymes and GSH level in rat stomach and colon mucosa and in liver in the presence of the non-steroidal anti-inflammatory drug amtolmetin guacyl (AMG, **49**). An increased SOD activity and a tendency to a decreased Fe/ascorbic acid-induced lipid peroxidation were observed in stomach and colon mucosa in the presence of AMG. In the liver, celecoxib decreased spontaneous Fe/ascorbic acid-induced lipid peroxidation while SOD activity was enhanced only in the presence of AMG. This study suggested that the beneficial effects of celecoxib might be due to their antioxidant and metal-chelating abilities [39]. Another study published in 2011, showed alterations of oxidant/antioxidant status and histopathological changes in tissues of young rats treated with celecoxib [40]. It was observed an increase in lipid peroxidation due to induction of oxidative stress by celecoxib treatment. Changes in CAT activity were observed which may be a direct antioxidant effect of celecoxib or a compensatory mechanism to overcome the excess production of H_2O_2 and free radicals. Celecoxib was also shown to induce superoxide anion generation, which caused a decrease in SOD activity. Among the celecoxib analogues **50a-e** and **51a-e** (Fig. 10), derivative **50a**, having an ethyl group at the *N*-position of the sulfonylthiourea structure, showed significant analgesic and promising anti-inflammatory activity with relatively reduced lipid peroxidation [41].

In the DPPH assay, at 10^{-3} M concentration level, the scavenging activity of sulfonamido bispyrazoles **52** and **53** (29 and 23 %, respectively) was almost the same as

that of sulfonylureido and thiosulfunylureido derivatives **55** and **57** (25 and 27%, respectively) (Fig. 10). Derivatives **54** and **56** showed mild scavenging activity (12 and 16%, respectively) when compared to the other tested compounds. At 10^{-4} M concentration pyrazoles **52**, **53** and **55** were able to exhibit moderate to good scavenging activity (17, 19 and 13 %, respectively) when compared to BHT **7** (20 %). It is important to notice that the most active compounds **52**, **53** and **55** present a reduced pyrazole ring [42].

In DPPH method, acetoxysulfonamide pyrazole **58**, substituted 4,5-dihydropyrazole-1-carbothioamide **59** and 4,5-dihydropyrazole-1-isonicotinoyl derivative **60** (Fig. 10) acted as antioxidants at low concentrations (0.25 mg/mL) in the following order **59**> **60**> **58**, while converted to pro-oxidant compounds at higher concentrations (0.5 mg/mL, 0.75 mg/mL and 1 mg/mL) [43].

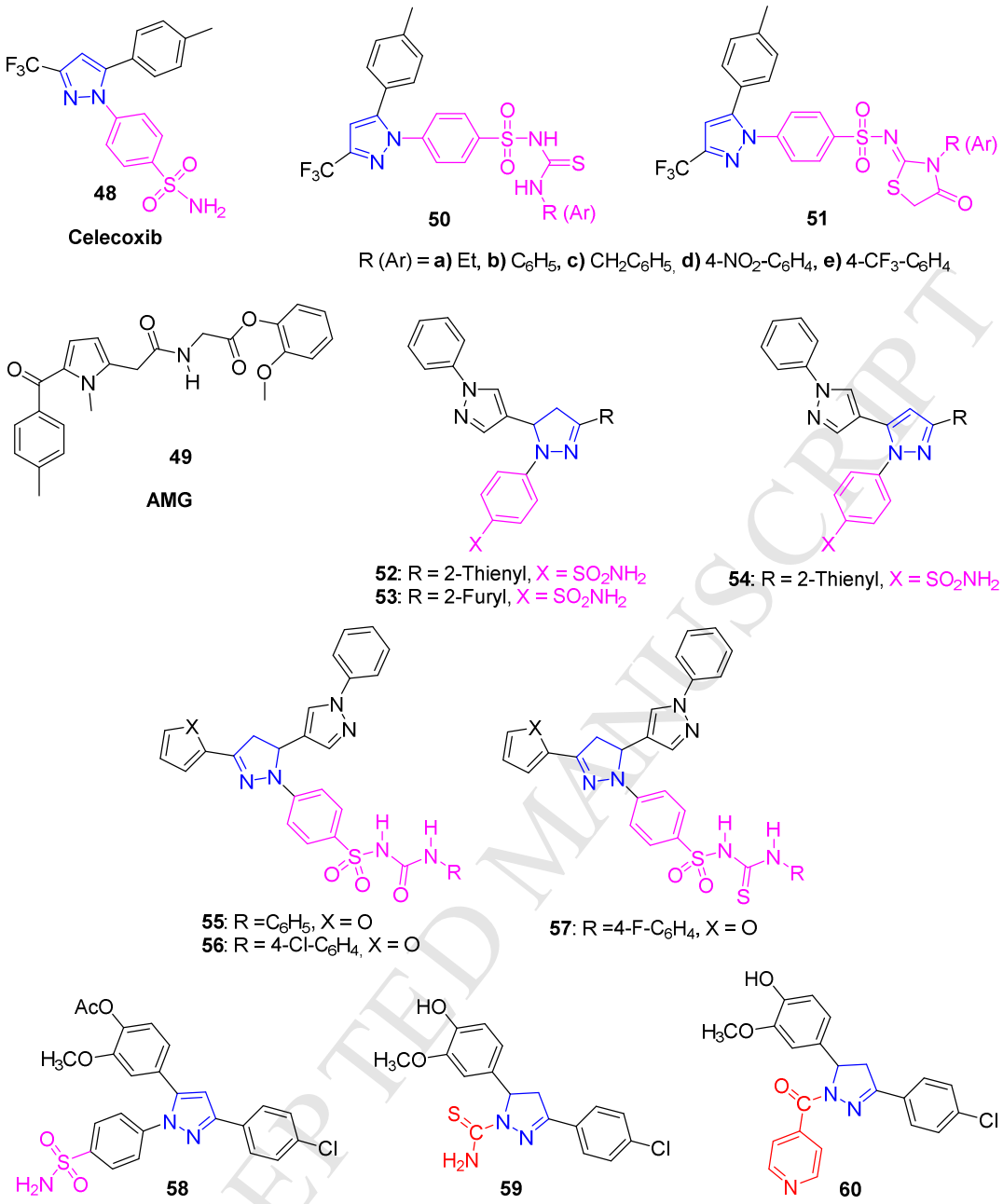


Fig. 10. Structures of celecoxib **48**, the non-steroidal anti-inflammatory drug amtolmetin guacyl **49** and celecoxib analogues **50-60** [37,41,42, 43].

2.1.8. Rimonabant and other 1-/3-/4-/5-pyrazolecarboxamides

Rimonabant **61** (Fig. 11), a well-known pyrazole and CB1-receptor antagonist, promoted angiotensin II type 1 receptor down-regulation, reducing angiotensin II-mediated ROS production and NADPH oxidase activity and vascular ROS burden. These effects led to improved endothelial function *in vivo*, indicating beneficial direct vascular effects [44]. Wassmann and co-workers also demonstrated that rimonabant reduced angiotensin II-mediated NADPH oxidase activity *in vivo* and *in vitro* thus

decreasing vascular oxidative stress [44]. This effect of rimonabant seems to be due to CB1-R inhibition, which significantly inhibited angiotensin II-mediated ROS production. They also found that like rimonabant, the CB1-receptor inverse agonist AM251 **62** also led to significant down-regulation of the AT1-receptor. On the other hand, the competitive CB1-receptor agonist CP-55,940 **63** caused an up-regulation of AT1-receptor.

The antioxidant activity of amido-linked benzoxazolyl/benzothiazolyl/benzimidazolyl-dihydropyrazoles **64a-c**, **65a-c** and **66a-c** and amido-linked benzoxazolyl/benzothiazolyl/benzimidazolyl-pyrazoles **67a-c**, **68a-c** and **69a-c** (Fig. 11) was screened by DPPH, nitric oxide and hydrogen peroxide methods [45]. Derivative **67b** showed excellent RSA in all three methods when compared with AA **5**. Compounds **67a** and **68b** exhibited good activity whereas **67c** and **68a** displayed moderate activity. Compound having the methyl substituent on the phenyl ring was more active than unsubstituted and chloro-substituted compounds. The pyrazolyl derivatives **67a-c** exhibited greater activity than pyrazolinyl derivatives **64a-c**. Moreover, benzoxazolyl amido-linked derivatives showed greater activity than the benzothiazolyl and benzoimidazolyl amido linked ones. In general, the RSA increases with increase in concentration in all three methods. Amido-linked bis-heterocycles-benzoxazolyl/benzothiazolyl/benzimidazolyl-pyrazoles and isoxazoles **76-81** and their dehydro-derivatives **70-75** (Fig. 11) were tested for antioxidant activity by the three methods above mentioned at three different concentrations 50, 75 and 100 μg/mL using AA **5** for comparison [46]. Aromatized compounds **76-81** exhibited greater activity than the corresponding non-aromatized derivatives **70-75**. The compounds **76b** and **79b** showed the higher FRSA in all three methods when compared with AA **5**. Compounds **76a**,**c**, **77b**, **79a**,**c** and **80a,b** exhibited good activity whereas compounds **77a**,**c**, **80c**, and **81a,b** displayed moderate activity. Regarding the structure-activity relationship it was found that in general amido-linked benzoxazolyl pyrazoles **76** and isoxazoles **79** displayed higher FRSA than benzothiazolyl pyrazoles **77** and isoxazoles **80**, benzimidazolyl pyrazoles **78** and isoxazoles **81**. Moreover, the compounds having the benzothiazolyl moiety **77** and **80** were more active than those with benzimidazolyl moiety **78**, **81**. Compounds having methyl substituent on the phenyl ring presented higher activity than unsubstituted and chloro-substituted ones, which may be due to the electron-donating effect of the alkyl substituent.

Fifteen 3-(pyridin-4-yl)-1*H*-pyrazole-5-carboxamide chalcones **82a–o** (Fig. 11) exhibited moderate RSA against DPPH$^{\bullet}$ radical. The most potent compounds were **82f** and **82j** containing thiophene and *ortho*-chlorophenyl units, respectively. Compounds **82a-o** were also tested for hydrogen peroxide RSA and compounds **82g**,**k**,**m** showed better scavenging activity than the others. Compounds **82b**,**e**,**j**,**n,o** also showed good scavenging activity while nitro (**82l)** and *N*,*N*-dimethylamino (**82h)** groups at *para*-position of phenyl ring slightly reduce the scavenging activity. However all the synthesised compounds showed higher activity than the parent pyrazole and chalcone in both DPPH and hydrogen peroxide scavenging assays [47].

5-Aryl-3-cyclopropyl-4,5-dihydropyrazole derivatives **84a**-**p** (Fig. 11) revealed a significant concentration dependent FRSA toward superoxide radical anion. Most of the carbothioamide derivatives displayed higher activity than the corresponding carboxamide derivatives, probably due to the presence of S atom which was reported to act as good radical scavenger. The highest activity was observed with the carbothioamide **84e** and the carboxamide **84n**, which contain chloro or *N*,*N*-dimethyl substituents at the *para*-position of the phenyl ring, compared to rutin **21** as a standard. The pyrazoline derivatives exhibited their antioxidative behaviour in the riboflavin-NBT system assay and no significant effect in the NO-based cell assay [48].

2.1.9. Pyrazolylcarbohydrazides

Pyrazoylcarbohydrazides **85** and **87** (Fig. 12) exhibited ability to scavenge DPPH$^{\bullet}$ radical [49]. Compound **87bf** (R^1 = Ph/ R^2 = 4-Tolyl, R^3 = H) was the most potent, being active at the concentration 47.57 μg/mL. The percentage of inhibition is concentration-dependent and compounds **85a-f** presented relevant percentage of inhibition, when compared with BHT **7** (91.2% inhibition), at a concentration of 250 μg/mL, with values ranging from 65.8–90.4 %. However, the new semicarbazone **87bf**, prepared from **85b**, was capable of inhibiting a higher percentage of 97.7 % at the same concentration. These compounds showed good antioxidant activity probably due to the presence of a π conjugated system in their structures, in addition to the other important structural features such as fluorine atoms, the hydroxyl group and the semicarbazone moiety.

Thirteen 1,5-diarylpyrazole hybrids with vanillin (Fig. 12) were tested in two different antioxidant assays [50]. All the compounds exhibited a better DPPH RSA than vanillin

and vanillic acid, in which compound **88g** was the most active (EC_{50} = 2.34 mM) but less active than AA **5**. The antioxidant activity is due to the phenolic hydrazone moiety.

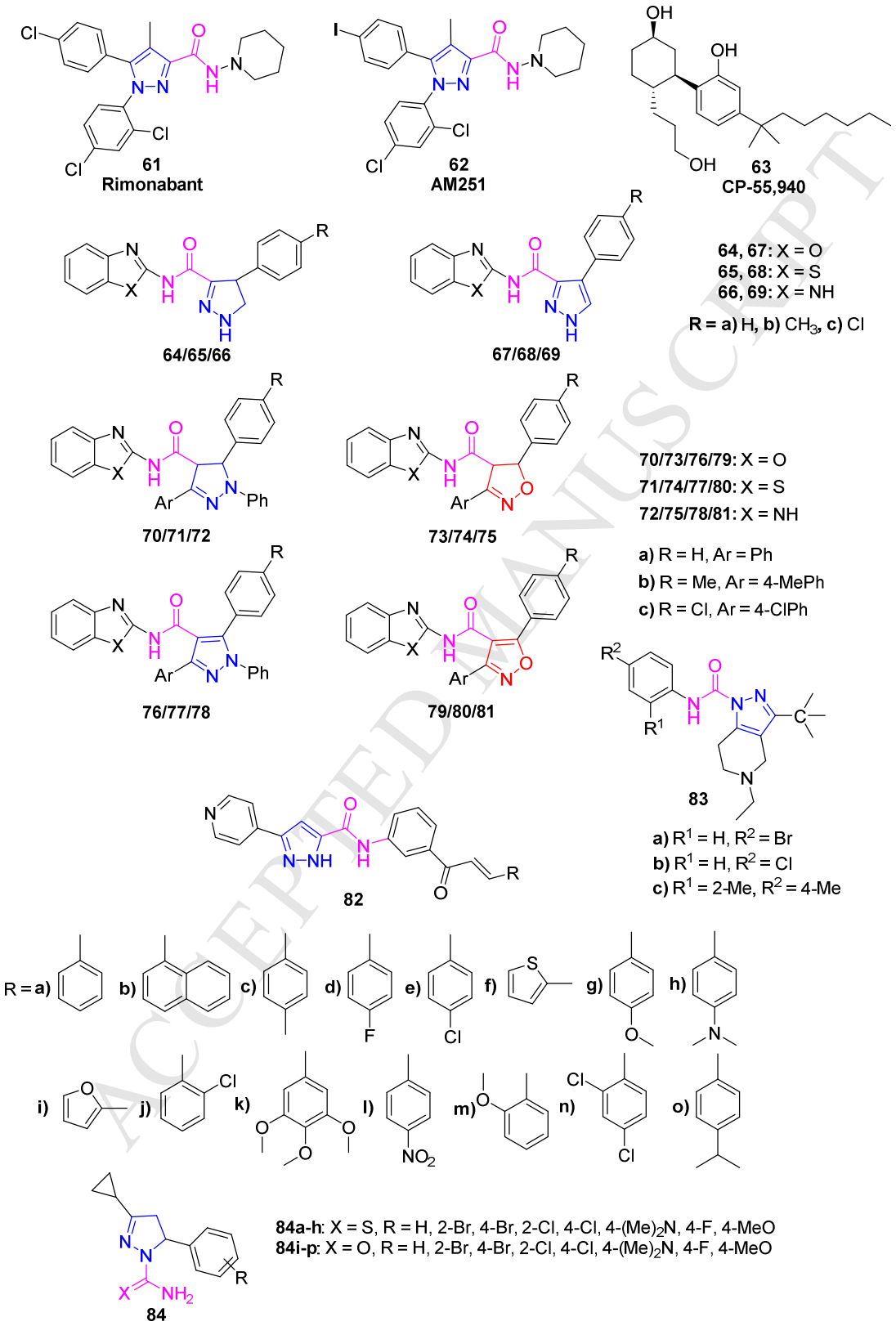


Fig. 11. Rimonabant **61**, AM251 **62**, CP- 55,940 **63** and other amino-linked pyrazole derivatives **64-84** [44,45,46,47, 48].

The hybridization of vanillin with 1,5-diarylpyrazole derivatives increases the antioxidant activity of this phenolic compound due to the conjugation of both scaffolds. The ORAC assay corroborated the results of DPPH assay and indicated that hybrids had an antioxidant effect ranging from 401 to 1076 trolox equivalents/g of compound. In this case, compound **88b** was the best antioxidant (1076 trolox equivalents). Thermodynamic and kinetic studies indicated that the most feasible mechanism for the antioxidant activity demonstrated by these compounds consists in the hydrogen atom transfer (HAT) abstraction of the phenolic hydrogen due to the formation of a stable transition state through the most rapid and exergonic path, while the sequential proton loss electron transfer (SPLET) mechanism is the most significant at higher pH values. It was not possible to establish any structure-activity relationships since the antioxidant activity is due to the guaiacol moiety and the substitutions of phenyl ring slightly interfere in the global effect.

The antioxidant activity of ten *N*'-arylidene pyrazole-3-carbohydrazides **89a-j,** including different hydroxylated patterns as a key feature for antioxidant capacity (Fig. 12), was evaluated by means of DPPH and FRAP in vitro assays [51]. The 3,4-dihydroxylated derivative **89b** and compounds bearing a hydroxy group at 4-position of the phenyl ring of the hydrazone moiety (**89c**,**g**,**i**,**j**) are potent antioxidant entities, being compound **89g** (a syringaldehyde derivative) the most active, with and IC_{50} similar to that of the effective α-tocopherol **6** and was more potent than quercetin **16**. The compounds seems to exert their action by HAT and single electron transfer (SET) mechanisms; after hydrogen abstraction caused by DPPH by a HAT pathway, the phenoxy radical can be stabilized through resonance within the phenyl ring and even with the hydrazone moiety. On the other hand, the hydrazone could donate an electron to $DPPH^{\bullet}$ radical (SET pathway) generating a cationic-radical species, which would eventually lose a proton to produce the identical radical intermediary as the HAT path. However, the possibility of compound **89b** to coordinate with iron, a well-known antioxidant mechanism of catechol derivatives and polyphenols, was not discarded. The lack of activity observed for compound **89a** corroborates the idea that the hydroxy group at *para*-position is a necessary but not a sufficient requirement for exhibiting antioxidant effect. On the other hand, the significant activity of cinnamaldehyde derivative **89h** (90% of DPPH scavenging), without substituents at phenyl ring, was explained by the participation of additional hydrogen abstractions in other positions, such as the amidic hydrogen, conducting to a stabilized radical intermediate.

Superoxide anion RSA of compounds **90a-q** (Fig. 12) was studied along with the standard *n*-propyl gallate **13** [52]. Almost all the tested compounds have exhibited moderate to good activity. SAR studies indicated that activity generally increases with the number and strength of oxygen containing functional groups. In fact, compound **90k** (dihydroxy derivative; 98.34%) was more active than **90j** (monomethoxy derivative; 44.90%), which was more active than **90a** (bearing no substituent). The substitution of an alkoxy group with hydroxy group on the ring increased the activity (**90l** was more active than **90m**) probably due to steric effects. Among the halogenated derivatives the relative FRSA was observed in the following order: *meta* > *ortho* > *para.*

Hydrazone incorporated pyrazoles and 1,2,3-triazoles **91a-d** and **92a-g** (Fig. 12) showed inhibitory activity, in DPPH assay, ranging from 51.8-72.0%, which was lower than that of BHT **7** (90.42 %) [53]. Among the tested compounds, derivatives **91a** (70.6%), **92d** (70.2%) and **92e** (72.0%) exhibited good scavenging activity. In common these compounds present one or two chlorine atoms in their structure which may enhance their RSA. On the other hand, compounds **92f** (69.1%) and **92g** (64.1%) which present EWG at 3- and 4-positions, respectively, showed only moderate antioxidant activity. From the remaining compounds, derivative **92b** (64.5%) bearing a 4-methoxy group showed better activity compared to **91b** (60.9%), **91c** (61.8%), **91d** (59.6%) and **92a** (51.8%).

2.1.10. Aryl/heterylsulfonylpyrazoles

Antioxidant activity of compounds **93-104**, bis-heterocycles **105-108**, bispyrazoles **109** and bis(pyrazolines and pyrazoles) **111** and **112** (Fig. 13) was evaluated by DPPH, nitric oxide and hydrogen peroxide methods [54,55,56,57]. Compounds **95b**, **97b**, **99b**, **101b** and **103b** showed good RSA in all three methods in comparison with AA **5**, suggesting an important role of the EDGs such as methyl and methoxy in the benzene ring. In general, the aromatized compounds **99-104** were more active than the respective dihydro compounds **93-98** and the isoxazole in combination with oxazoline **103** exhibited higher activity than the compounds having the pyrazole combined with oxazoline **99**, **101**, which may be due to the presence of two oxygen atoms in the structure of **103**. The FRSA of the most active compounds, in the three methods, increases with the concentration increase [54]. From the bis-heterocycles, the aromatized compounds **107** and **108** displayed greater activity than the respective dihydro-derivatives **105** and **106**. Regarding the heterocyclic pharmacophore, isoxazolyl

oxadiazoles showed comparatively higher RSA than the pyrazolyl oxadiazoles.

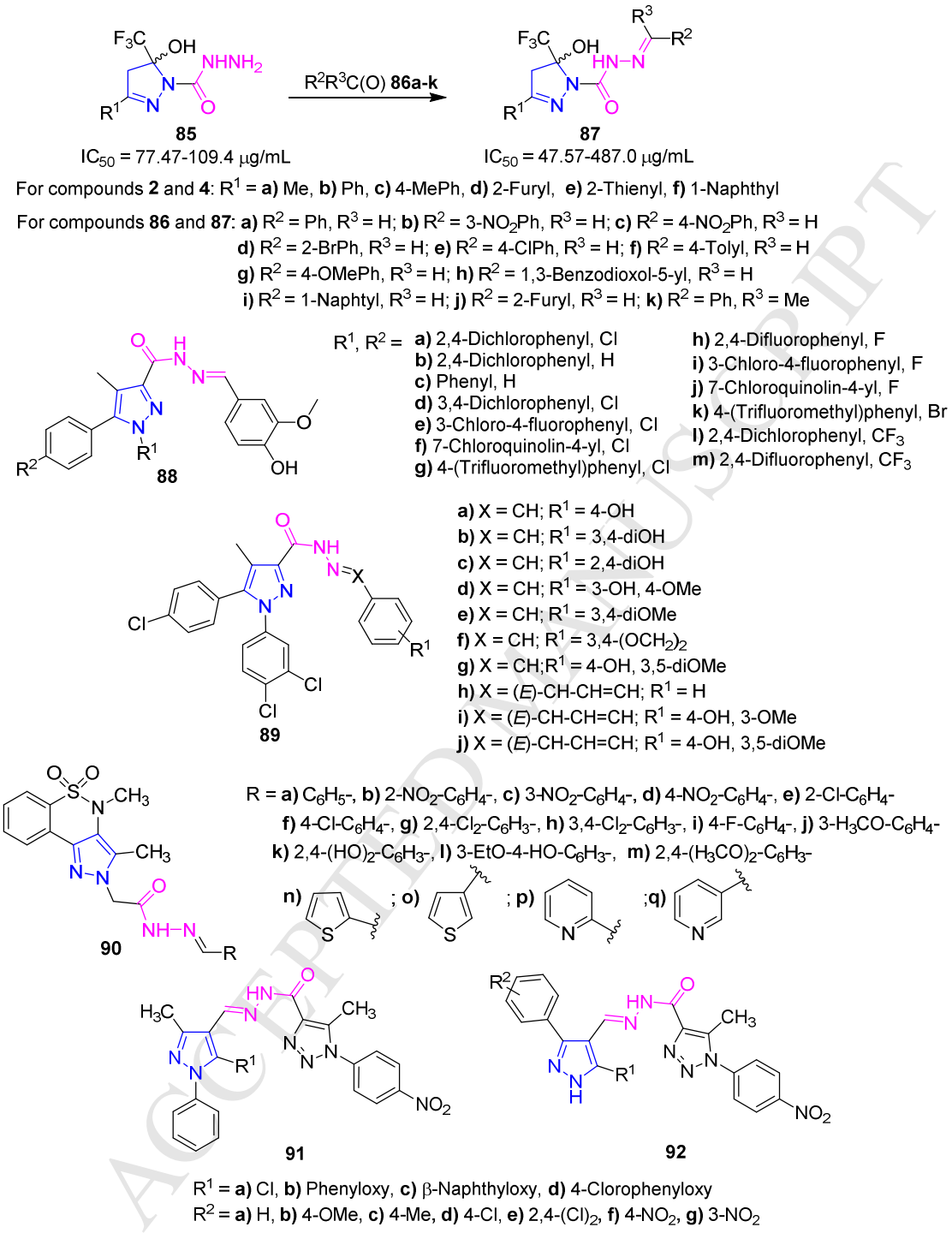


Fig. 12. Pyrazolylcarbohydrazides **85-92** [49,50,51,52,53].

Unsubstituted and methyl substituted compounds **107a**,**b** and **108a,b** exhibited higher activity than the corresponding chloro-substituted compounds **107c** and **108c**. Besides, RSA increases with increase in concentration in all the three methods [55].

Bispyrazole derivatives **109a-d** showed considerable antioxidant activity. Compound **109d** bearing a methoxy substituent on the aromatic ring was found to be the more active showing excellent FRSA compared to AA **5**, probably due to the positive mesomeric effect of this substituent. The FRSA was found to increase with increase in concentration. The IC_{50} value for compound **109d** in DPPH method was found to be 57.08 µg/mL whereas the IC_{50} for AA **5** was 59.65 µg/mL at 100 µg/mL. The presence of the pyrazole core as the heterocyclic moiety delivers enhanced antioxidant ability to these compounds when compared to the analogous pyrrole derivatives **110a-d** [56].

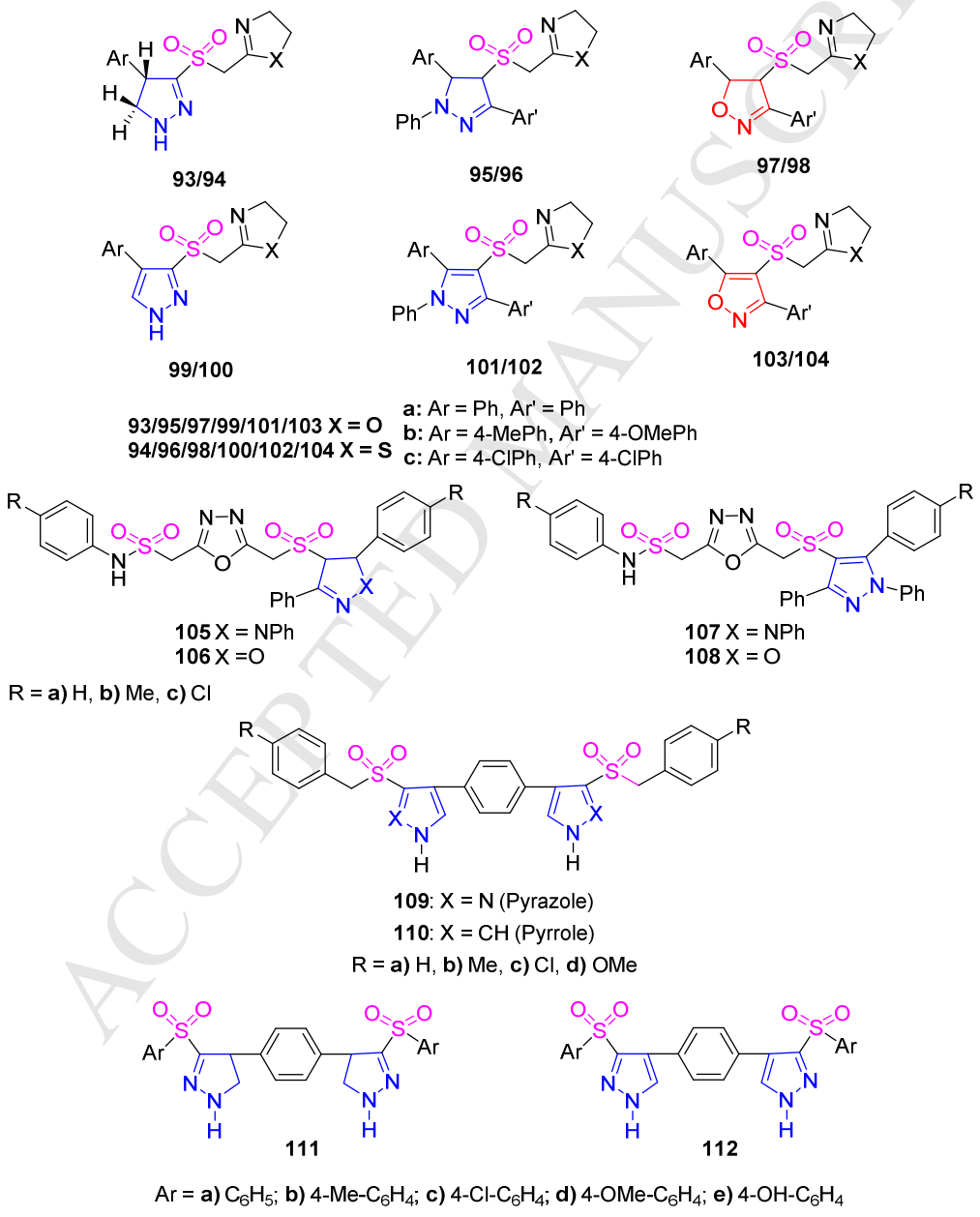


Fig. 13. Aryl/heterylsulfonylpyrazole derivatives **93-112** [54,55,56,57] .

1,4-[Bis(3-arylsulfonyl)-1*H*-pyrazol-4-yl]benzenes **112a-e** exhibited better antioxidant activity than 1,4-[bis(3-arylsulfonyl)-4,5-dihydro-(1*H*-pyrazol-4-yl)]benzenes **111a-e** [57]. As in previous studies [56] EDGs enhanced the antioxidant activity since derivatives having methyl **112b**, methoxy **112d** and hydroxy **112e** substituents on the aromatic ring showed higher activity than the other substituents probably due to positive inductive and mesomeric effects.

2.1.11. Curcumin-templated pyrazole derivatives

Recently, Sanz and coworkers made a comprehensive review of pyrazoles derived from curcumin, curcuminoids and hemi-curcuminoids together with some of their biological properties [58]. These type of compounds exhibited diverse biological activities including antioxidant activity. Curcumin-templated azoles **114a-f** and **115** were tested for antioxidant activity based on DPPH, FRAP and β-carotene bleaching assays and were found to be better antioxidants than curcumin **113** (Fig. 14) [59,60]. In DPPH assay the antioxidant capacity of azoles **114a-f** and **115** was seen to be in the order **115** > **114a** > **114c** > **114b** > **114e** > **113** >**114f** > **114d** with the isoxazole **115** exhibiting higher activity than the pyrazoles **114a-f** and curcumin **113.** Among the azoles tested, compounds **115** and **114a-c**,**e** have better antioxidant capacity than curcumin **113**. Typical EC_{50} values of curcumin **113**, 3,5-bis-(4-hydroxy-3-methoxystyryl)pyrazole **114a**, and 3,5-bis(4-hydroxy-3-methoxystyryl)isoxazole **115** were 40 ± 0.06, 14 ± 0.18, and 8 ± 0.11 µmol, respectively. The antioxidant capacity, evaluated by the FRAP method and β-carotene bleaching assay showed a similar trend as that seen in the case of DPPH assay. Thus, heterocyclization of curcumin seems to result in improved antioxidant activity. SAR analysis suggested that EDGs in the *N*-phenyl group of the pyrazole, as in **114c**, leads to a better activity than that in the parent *N*-phenylpyrazole curcumin **114b** and the presence of EWG, as in **114d**, leads to a lower activity. The present results are in good agreement with those reported very recently by Jha and co-workers [61] based on their extensive electrochemical cyclic voltammetric studies in which the azole derivatives of curcumin have showed better antioxidant properties than curcumin. These results, based on the DPPH, FRAP and β-carotene bleaching assays, also provided further support to the observations of Puneeth and Chandrashekariah [62] that among curcumin-derived *N*-arylpyrazoles, the presence of EDGs on the aryl ring provides improved antioxidant activity.

Compound **114b**, also known as CNB-001[63] has shown the ability to scavenge various free radicals and protect DNA against H_2O_2-induced oxidative stress. Through its antioxidant action this compound had a neuroprotective effect on biochemical and apoptotic markers against rotenone-induced SK-N-SH cellular model of Parkinson's disease [63].

In DPPH assay, the curcumin-based pyrazoles **116a-g** (Fig. 14) have shown antioxidant activity in the order **116b** >**116a** > **116f** > **116c** > **116d** > **116e > 116g**. The presence of hydroxy and methoxy substituents on the terminal phenyl rings seems to improve the antioxidant capacity as against the presence of a hydroxy group alone, as in **116a** and **116c**. Similar results were obtained in the FRAP and β-carotene bleaching assays. Moreover, the antioxidant capacity of CNB-001 was superior to those of the CNB-001 analogues **116a-g** [64].

At 50 μM concentration curcumin-derived pyrazole **117c** presented the higher FRSA (89.2%) against DPPH while the other derivatives showed lower percentage of activity (**117a**, 64.1%; **117b**, 86.8%; **117d**, 81.2%) as compared to **117c** (Fig. 14) [65]. However all the compounds have higher FRSA than curcumin **113** (50.2%). Even at 10 μM concentration, **117c** (31.2%) is almost 6 times more potent than **113** (6.0%). It is obvious that the pyrazole core increased the activity of curcumin and in particular thiosemicarbazide (**117b**) and 2,4-dinitrophenyl hydrazine (**117d**) pyrazole derivatives showed better activity with 86.8% and 81.2%, respectively. At 50 μM concentration curcumin derivatives (**117a**, 88.8%; **117b** 90.2 %; and **117c**, 82.2 %) showed the higher scavenging ability against nitric oxide radical as compared to **113** (59.9%). However, the RSA of derivative **117d** (50.8%) was lower than that of **113**. At 2 μM concentration all derivatives (**117a**, 29.9%; **117b**, 32.3 %; **117c**, 31.2 %, **117d**, 15.5 %) showed higher FRSA than **113** (12.2 %). The results clearly show that pyrazole moiety has a considerable role in enhancing the antioxidant activity by involvement in the mechanism of FRSA. Regarding the superoxide RSA at 50 μM concentration (**117a**, 62.9%; **117b**, 90.0 %; **117c**, 89.2 %, **117d**, 58.9 %) and 2 μM concentration (**117a**, 20.2%; **117b**, 30.2 %; and **117c**, 32.2 %, **117d**, 14.9 %) all derivatives have demonstrated higher FRSA than **113** (42.2 % at 50μM and 13.9 % at 2μM). Compounds **117a-c**, having EDGs were found to possess higher superoxide RSA, in particular compounds **117b,c** which were the most active [65].

Asymmetrical pyrazole curcumin analogues **118a-g** have shown *in vitro* hydrogen peroxide, DPPH, ferrous reducing power and nitric oxide scavenging activities [66]. Against hydrogen peroxide, compounds **118e** and **118b** were the most active and exhibited excellent to good scavenging activity (88.45% and 71.12 %, respectively) as compared to BHT **7** (88.42 %). Compounds **118b,d**,**f**,**g** showed good DPPH FRSA (42.32-36.80 %) as compared to AA **5** (42.98 %). With exception of compounds **118a,f**, that showed only moderate activity (33.33 %) the others, **118b-e** and **118g** showed excellent ferrous reducing power activity (55.55–44.44 %) as compared to AA **5** (42.44 %), and all the compounds showed better nitric oxide RSA (77.94-32.35 %) when compared to AA **5** (32.32 %). The variation in the proton-electron transfer by the derivatives, due to the difference in their structures, may explain the wide variation in the FRSA of these compounds and do not allows the establishment of structure-activity relationships [66].

Other bis-2-pyrazolines **119a-c** (Fig. 14) obtained from curcumin have demonstrated variable IC_{50} values in DPPH assay. The most active compound was the unsubstituted derivative **119a**, however all the compounds were less active than curcumin **113** and AA **5** used as references [67].

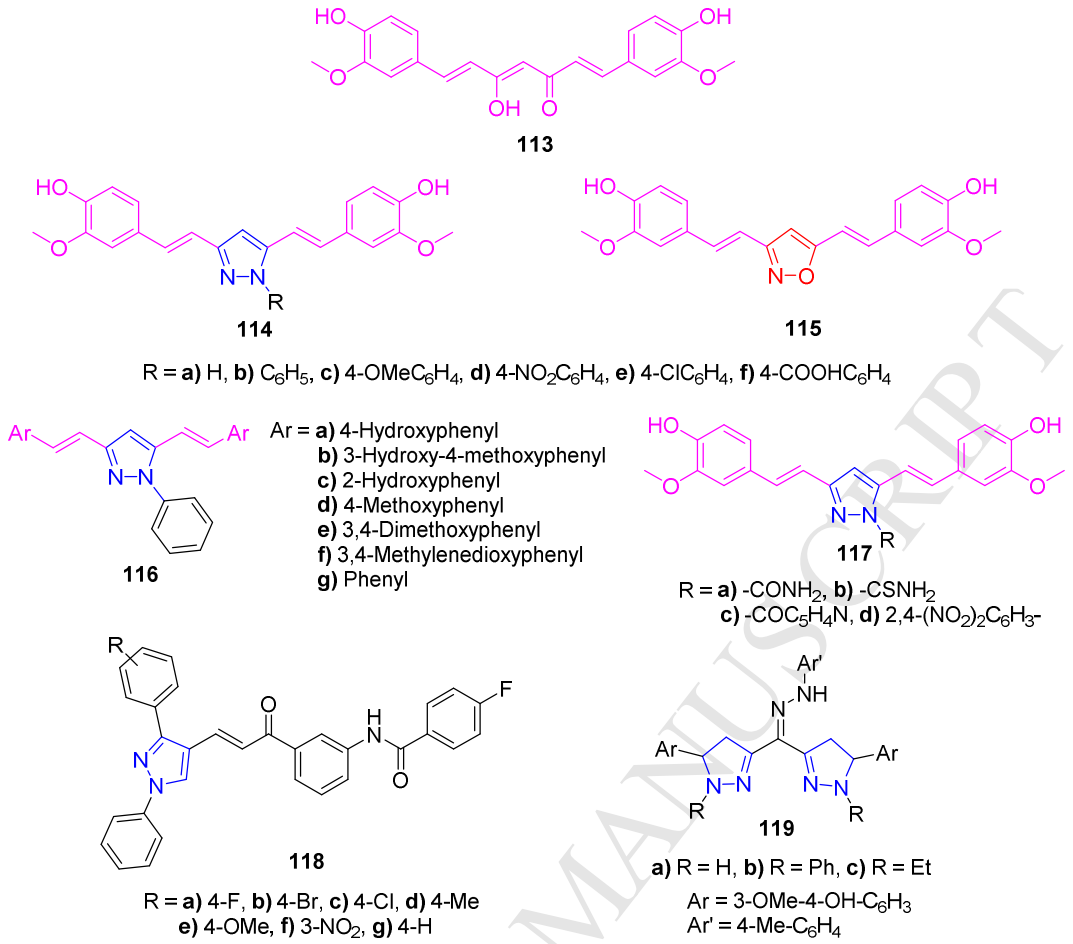


Fig. 14. Curcumin **113** and curcumin-derived pyrazoles and isoxazoles **114-119** [59,61,62,63,64,65,66,67].

2.1.12. Pyrazolyl-2H-chromen-2-ones and conjugates

The antioxidant activity of a series of 4-methylcoumarin (also known as 4-methyl-2*H*-chromen-2-one) derivatives containing 2-pyrazoline moiety was evaluated in AAPH-induced oxidation of DNA and in trapping DPPH$^{\bullet}$ and ABTS$^{+\bullet}$ radicals, respectively, using xanthotoxol **11**, a good natural coumarin antioxidant, as positive control [68]. Among coumarin derivatives, **120a,b, 121a,b** and **122a-c** (Fig. 15) exhibited the termination of radical propagation-chains in AAPH-induced oxidation of DNA having higher activity than xanthotoxol **11**. The antioxidant activity is largely dependent on the number of hydroxy groups on the phenyl ring. The 5-catechol substitution, that increases the stabilization of the semiquinone radical by intramolecular hydrogen bond, and the 1-unsubstitution of the 4,5-dihydroxypyrazole were found to enhance the antioxidant activity of these coumarin derivatives. The hydrogen atom of the 1-unsubstituted dihydropyrazole coumarins can be abstracted by radicals, resulting in a single electron that can be stabilized via resonance [68]. Among all the tested

compounds, derivatives **120b** and **122a** were found to be promising lead compounds suitable for further development of new antioxidants.

Coumarin appended 4-formylpyrazoles **123a-e**, (Fig. 15), showed promising DPPH FRSA but were less potent than BHT **7** [69]. At lower concentrations, all the compounds exhibited poor FRSA however a gradual increase in this activity was observed with the increase in the concentration. Compound **123d**, having chlorine at the *para*-position of the phenyl ring was the most active of this series followed by **123a** and **123e** that have shown moderate FRSA in comparison with BHT **7**. The presence of EDGs in the aromatic ring and the stereochemical factors associated to the substitution at *ortho*-position might be the cause of the weak activity of compounds **123b** and **123c**.

From the coumarin based bis(formylpyrazole) derivatives **124a-h** (Fig. 15), compounds **124g** and **124h** having $CONH_2$ and $CSNH_2$ in the pyrazole ring, respectively, showed better DPPH FRSA than AA **5** [70]. Compounds having no substitution **124a** or a methoxy group **124d** showed moderate activity while those having methyl **124c** and chloro **124f** substitution showed similar antioxidant activity as AA **5**. The compounds with a methyl group at *meta*-position **124c** or a fluoro substitution at *para*-position **124e** showed lower antioxidant activity than AA **5**. Compounds **124g** and **124h** also exhibited remarkable FRSA, against $HO^{\bullet}$ radical, significantly higher than that of BHA **8**. Compound **124d** having the methoxy substituent showed excellent activity while moderate activity was found for compounds **124a**,**b** and **124f**.

All the pyrazolylcoumarins **125a-k** (Fig. 15) showed FRSA using DPPH method [71]. Derivatives **125d** [R = 2,4-$(Cl)_2$] and **125k** (R= 4-OH) were found to be the most active antioxidants in this series. The IC_{50} of these compounds was 1.03 ± 0.067 mM for **125d** and 1.07 ± 0.088 mM for **125k**, as compared with AA **5** (0.026 ± 0.022 mM) and BHT **7** (0.13 ± 0.012 mM). The compound **125c** (R=4-Cl) was found to be active among the tested compounds not only as antioxidant but also as anti-inflammatory agent indicating that the antioxidant activity influences the anti-inflammatory activity.

3-(5-Aryl-4,5-dihydro-1*H*-pyrazol-3-yl)-4-hydroxy-2*H*-chromen-2-ones **126a**,**b**,**d**,**e**, exhibited higher antioxidant activity than trolox **10**, in DPPH method, while the pyrazoline bearing a *p*-methoxy substituent in the phenyl ring exhibited enhanced antioxidant activity [72]. As for DPPH scavenging, dyads coumarin-pyrazolines **126** and **127** have shown higher capacity to quench $ABTS^{+\bullet}$ radical as compared to the synthetic antioxidant trolox **10**. Increasing the concentration of these compounds to about 1 μM the percentage of inhibition in DPPH assay reached 90% for all of them,

thus indicating that substituents on the aryl group do not have significant influence in the antioxidant activity.

Nine pyrazolylcoumarins **128** and **129a-h** were screened for antioxidant activity by inhibiting AAPH-, Cu^{2+}/GSH- and $^{\bullet}OH$-induced oxidation of DNA. It was found that less phenolic hydroxy groups can enhance the abilities of pyrazolylcoumarins to protect DNA against the oxidation. Even compounds **128** and **129a,b** without phenolic hydroxy group attached act as antioxidants. However the presence of double phenolic hydroxy groups at either *ortho*-, *meta*-, or *para*-positions are able to increase the abilities of pyrazolylcoumarins to inhibit Cu^{2+}/GSH-induced oxidation of DNA. Moreover, the evaluation of the scavenging activity against the $ABTS^{+\bullet}$, $DPPH^{\bullet}$ and galvinoxyl$^{\bullet}$ radicals suggested that double phenolic hydroxy groups were more beneficial for enhancing the abilities of these pyrazolylcoumarins to quench the aforementioned radicals. Therefore, these pyrazolylcoumarins exhibited powerful antioxidant effectiveness even in the case of less phenolic hydroxy groups involved [73]. SAR analysis revealed that the presence of an EDG at *para*-position, as in the case of compounds **129b** and **129e**, is not beneficial for enhancing the ability to inhibit $^{\bullet}OH$-induced DNA oxidation. On contrary, the presence of the hydroxy group in the *ortho*-position, as in **129c** and **129h**, can strongly improve the antioxidant effectiveness. Compounds **129a** and **129b** were not able to inhibit AAPH-induced oxidation of DNA while the antioxidant effectiveness of **128** was ascribed to the introduction of ferrocene moiety. The antioxidant effectiveness is almost proportionally related to the number of phenolic hydroxy group. Moreover, results obtained for compound **128**, which were close to that of compound **129d**, reveal that the antioxidant effectiveness of a ferrocene moiety is the same as a *meta*-phenolic hydroxy group. A benzene ring linked to the nitrogen of the pyrazole is also beneficial for increasing the antioxidant activity.

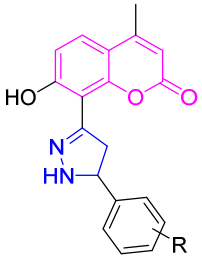
From the pyrazolylcoumarin derivatives **130a-l** (Fig. 15) compounds **130e** and **130g** showed the strongest DPPH RSA with IC_{50} 54.14–56.19 μg/mL [74]. The compounds with no substitution on phenyl ring **130a** and containing halogens **130c**,**k** were less active but still showed good scavenging effect with IC_{50} 64.75, 70.14 and 88.29 μg/mL, respectively. The other compounds displayed moderate to good scavenging activity. However all the compounds were less active than BHT **7** (46.95 μg/mL). The compounds substituted with EDGs on the indenone and phenyl rings **130e-h** exhibited excellent activity with IC_{50} value 53.75–62.30 μg/mL but were less active than EDTA

14 (44.11 μg/mL). The best reducing power was presented by **130g** containing two methoxy groups on indenone and a methoxy group on phenyl ring with IC_{50} 58.01 μg/mL near the IC_{50} of BHA **8** (50.00 μg/mL). The presence of the pyrazole ring endows these compounds with significant pharmacological interest [74].

A series of coumarinyl-pyrazolinyl substituted thiazoles exhibited significant mushroom tyrosinase inhibitory activities, better than kojic acid **15** [75]. In particular, derivative **131j** (Fig. 16) exhibited the most potent tyrosinase inhibitory activity with IC_{50} value 0.00458 ± 0.00022 μM compared with the IC_{50} value of kojic acid (16.84 ± 0.052 μM). The inhibition mechanism analysed by Lineweaver–Burk plots revealed that the type of inhibition of compound **131j** on tyrosinase was non-competitive. Docking studies revealed that compound **131a** showed the highest binding affinity (10.20 kcal/mol) with active binding site of tyrosinase. Some derivatives also showed good FRSA.

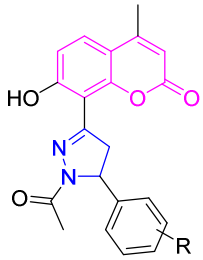
Also, coumarinyl pyrazolinyl thioamide derivatives **132a-q** showed good DPPH FRSA however at high concentration (100 μg/mL) [76].

The potential of the dyads **133** and **134** as $DPPH^{\bullet}$ radical scavengers was evaluated [77]. In general compounds of the pyrazolin-5-one series demonstrated higher activity than compounds of the pyrazole series, especially compounds **134a** (57%), **134d** (53%) and **134e** (69%) which exhibited moderate activity compared to AA **5** (96%). From the pyrazole series, compound **133e** exhibited the highest activity (69%) and **133b** showed moderate activity (55%).



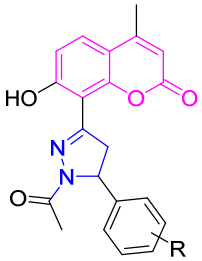
120a,b

a) R =3-NO_2
b) R = 3-OMe-4-OH



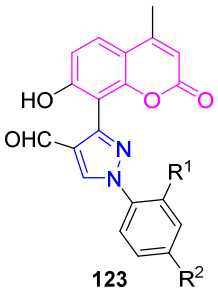
121a-d

a) R =3-NO_2
b) R = 3-OMe-4-OH
c) R = 2,4-$(OMe)_2$
d) R = 2-allyloxy



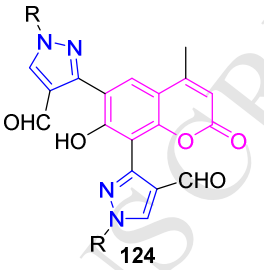
122a-c

a) R =3,4-$(OH)_2$
b) R = 2,4-$(OH)_2$
c) R = 2-OH



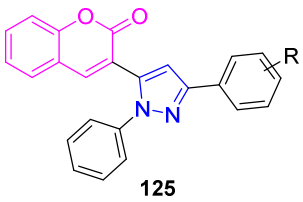
123

a) R^1 = H, R^2 = H
b) R^1 = OMe, R^2 = H
c) R^1 = Me, R^2 = H
d) R^1 = H, R^2 = Cl
e) R^1 = NO_2, R^2 = NO_2



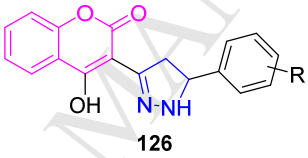
124

R= **a)** C_6H_5, **b)** 4-MeC_6H_4, **c)** 3-MeC_6H_4, **d)** 4-$OMeC_6H_4$
e) 4-FC_6H_4, **f)** 4-ClC_6H_4, **g)** $CONH_2$, **h)** $CSNH_2$

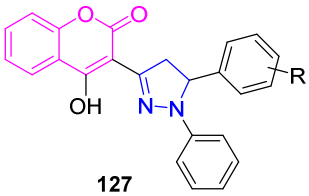


125

R = **a)** H, **b)** 4-OMe, **c)** 4-Cl, **d)** 2,4-$(Cl)_2$, **e)** 4-NMe_2
f) 3-NO_2, **g)** 4-Me, **h)** 3-OMe, **i)** 4-F, **j)** 2-NO_2, **k)** 4-OH

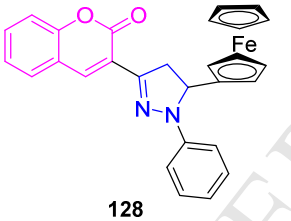


126

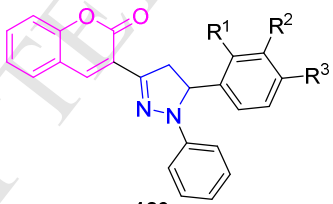


127

R = **a)** H, **b)** 4-F, **c)** 2,5-Me, **d)** 4-OMe, **e)** 4-NO_2

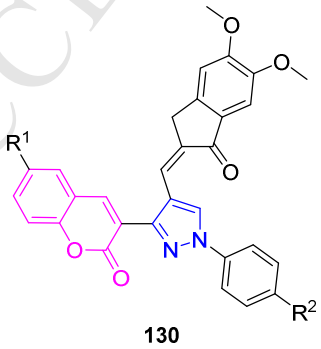


128



129

a) R^1 = H, R^2 = H, R^3 = H
b) R^1 = H, R^2 = H, R^3 = OMe
c) R^1 = OH, R^2 = H, R^3 = H
d) R^1 = H, R^2 = OH, R^3 = H
e) R^1 = H, R^2 = H, R^3 = OH
f) R^1 = H, R^2 = OMe, R^3 = OH
g) R^1 = H, R^2 = OH, R^3 = OH
h) R^1 = OH, R^2 = H, R^3 = OH



130

a) R^1 = H, R^2 = H
b) R^1 = Br, R^2 = H
c) R^1 = H, R^2 = 4-Cl
d) R^1 = Br, R^2 = 4-Cl
e) R^1 = H, R^2 = 4-Me
f) R^1 = Br, R^2 = 4-Me
g) R^1 = H, R^2 = 4-OMe
h) R^1 = Br, R^2 = 4-OMe
i) R^1 = H, R^2 = 4-NO_2
j) R^1 = Br, R^2 = 4-NO_2
k) R^1 = H, R^2 = 4-F
l) R^1 = Br, R^2 = 4-F

Fig. 15. Pyrazolyl-2*H*-chromen-2-one derivatives **120-130** [68,69,70,71,72,73,74].

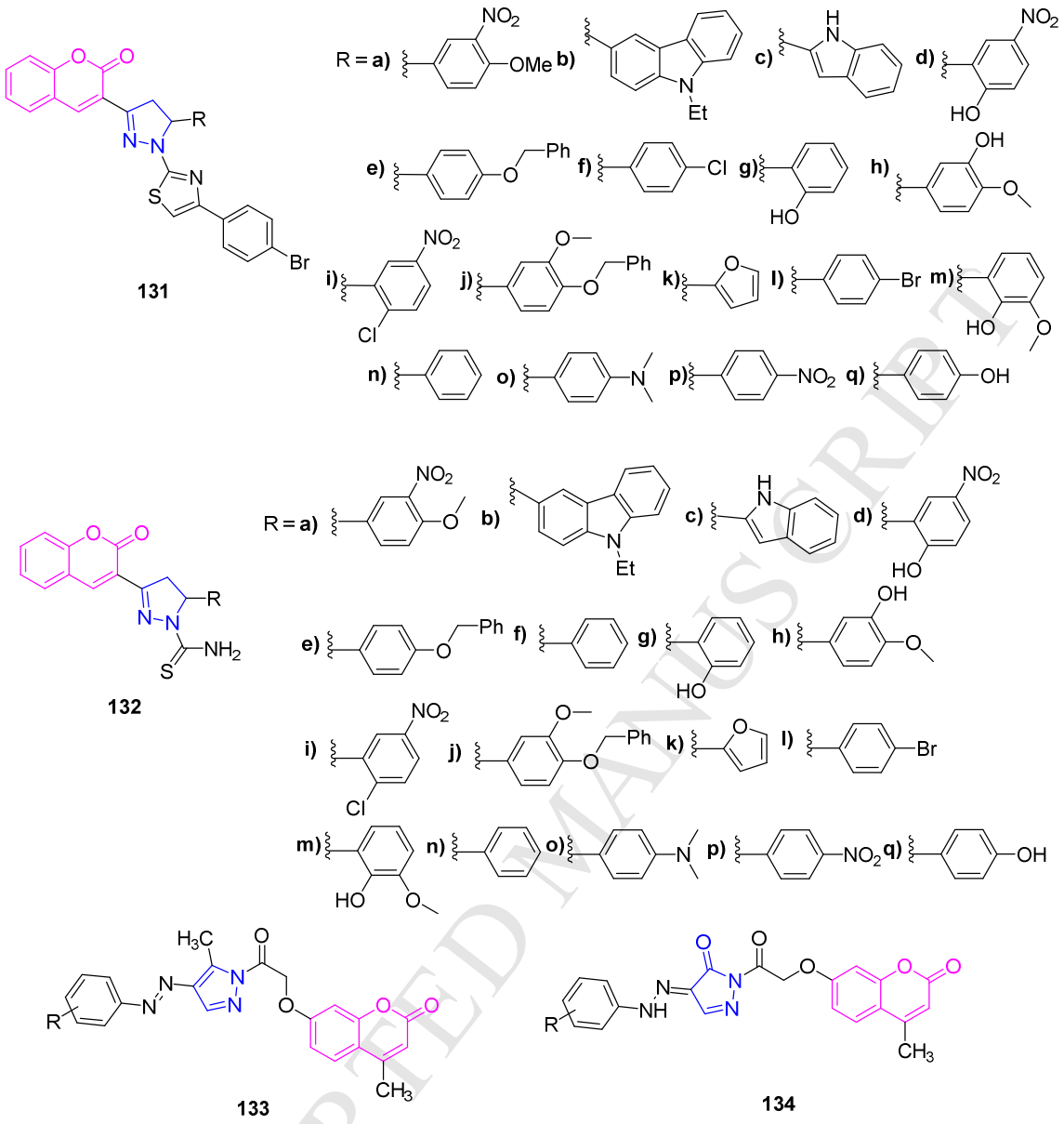


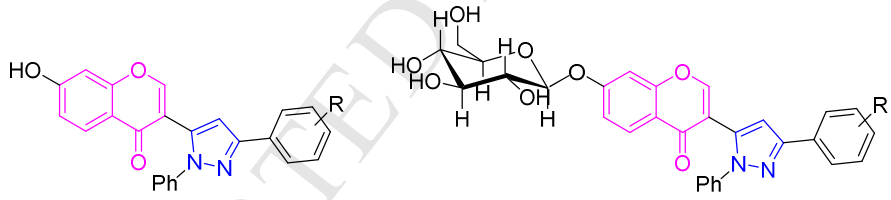
Fig. 16. Pyrazoyl-2*H*-chromen-2-ones **131-132**, arylazopyrazoles **133** and arylhydrazonopyrazolones **134** [75,76,77].

2.1.13. Pyrazolyl-4H-chromen-4-ones

A series of pyrazol-3-yl-4*H*-chromen-4-ones **135a-i** and their *O*-β-D-glucopyranosides **136a-i** (Fig. 17) were screened for their antioxidant activity [78]. All the tested compounds have shown high DPPH FRSA, when compared to AA **5** (98.03 % DPPH inhibition), ranging from 91.65±0.93 to 79.87±0.81, being active at 1 mg/mL concentration [78,79]. The *O*-glycosides have demonstrated higher FRSA than the corresponding aglycones in the following decreasing order: **136h** > **136b** > **136f** > **136a**

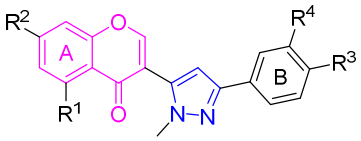
> **136c** > **136i** > **136g** > **136e** > **136d**. The most active compounds were those having one or more halogen atoms (Cl, Br) in the aryl ring or a strong EWG (NO_2), whereas the compounds with EDGs (OCH_3 or CH_3) were the less active.

The DPPH FRSA of another series of pyrazol-3-yl-4*H*-chromen-4-ones **137a-n** (Fig. 17) was evaluated at a concentration of 50 μg/mL by comparison with α-tocopherol **6** (>90 % inhibition; IC_{50} = 23.8±3.7 μM) [80]. Derivative **137j**, possessing a catechol moiety in the B-ring showed potent activity (>90 % inhibition; IC_{50} = 21.9±2.8 μM). Modifications on the chromone ring (A-ring) and on the phenyl ring at 3-position of pyrazole moiety (B-ring) revealed some interesting structure-activity relationships: (i) the introduction of a hydroxy group on the chromone ring (A-ring) did not significantly increase DPPH FRSA; in contrast the introduction of hydroxy groups in the B-ring increased DPPH FRSA. Thus, hydroxy groups on B-ring have a higher contribution for antioxidant activity than those on the A-ring. (ii) 3,4-Dihydroxy derivatives are more potent than the 4-hydroxy derivatives (**137j**, 21.9±2.8 μM versus **137i**, 10.3±0.5 μM; **137k**, 5.0±0.4 μM and **137l**, 19.8±3.2 μM), which is not a surprising result, since the catechol group is known to be an important structural feature to enhance the antioxidant activity.



135 **136**

R = **a)** H, **b)** 4-Cl, **c)** 4-Br, **d)** 4-Me, **e)** 4-OMe, **f)** 2,4-Cl_2, **g)** 3,4-Cl_2, **h)** 3-NO_2, **i)** 4-NO_2



137

a) $R^1 = R^2 = R^4 = H$; $R^3 = F$
b) $R^1 = R^2 = R^4 = H$; $R^3 = OMe$
c) $R^1 = R^2 = H$; $R^4 = R^3 = OMe$
d) $R^1 = R^3 = OMe$; $R^2 = R^4 = H$
e) $R^1 = R^4 = H$; $R^2 = R^3 = OMe$
f) $R^1 = H$; $R^2 = R^3 = R^4 = OMe$

g) $R^1 = OBn$; $R^2 = R^4 = H$; $R^3 = OMe$
h) $R^1 = OBn$; $R^2 = R^4 = H$; $R^3 = Cl$

i) $R^1 = R^2 = R^4 = H$; $R^3 = OH$
j) $R^1 = R^2 = H$; $R^4 = R^3 = OH$
k) $R^1 = R^3 = OH$; $R^2 = R^4 = H$
l) $R^1 = R^4 = H$; $R^2 = OMe$; $R^3 = OH$

m) $R^1 = OH$; $R^2 = R^4 = H$; $R^3 = OMe$
n) $R^1 = OH$; $R^2 = R^4 = H$; $R^3 = Cl$

Fig. 17. Pyrazolyl-4*H*-chromen-4-ones and their *O*-β-D-glucopyranosides **135-137** [78,79,80].

2.1.14. Furan/tiophene conjugated pyrazole derivatives

From a series 3,5-disubstituted-2-pyrazolines **138a-e** and 1,3,5-trisubstituted-2-pyrazolines **139a-e** (Fig. 18), five compounds **138d**,**e**, and **139a**,**d**,**e** showed DPPH RSA. Phenolic compounds were active while the other nonphenolic compounds were less active or inactive with exception of **139a**. The RSA order was **139e** > **138e** > **138d** > **139a** > **139d**. Accordingly, the strong DPPH scavenging activity of these compounds can be attributed in part to the phenolic OH present in their structures. These compounds have also shown nitric oxide RSA in the following order **139e > 139a > 138d > 138e > 139d > 138a > 138b**. Compound **139e** was the most active, in both assays, showing the importance of the hydroxy group at *para*-position of the phenyl ring [81].

Among the compounds **140** and **141** (Fig. 18), **140a-c**,**e**, and **141a**,**b**,**h**,**j** showed the best DPPH RSA, with significant activity when compared to AA **5** [82]. Compounds **140b** (86%), **140e** (88%), **141a** (86%) and **141h** (86%) were identified as potent antioxidants, with high percentages of inhibition, being almost as active as AA **5** (96%). The comparison between the RSA of 3,5-diaryl-2-pyrazolines **140b**,**e** and the 3,5-disubstituted 2-pyrazolines **141a,h**, showed that the introduction of the furan moiety at the 5-position of the pyrazoline ring does not have a significant effect on the RSA of these compounds. With exception of compound **140e**, the other three compounds have an EDG (OMe) as substituent in one of the phenyl ring attached to the pyrazoline moiety.

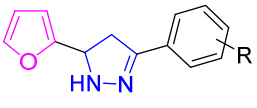
A series of furan-conjugated pyrazoles (Fig. 18) exhibited excellent DPPH RSA due to their hydrogen donating capacity. Compounds **142c**,**d** (R^1 = F), **142i**,**j** (R^1 = Cl) and **143c** (R^1 = R^2 = R^3= H) showed excellent activities compared to AA **5**. Compounds **142e-h** (R^1 = Me, OMe and R^4 = H, Me) showed moderate activities. Compounds **142a,b** (R^1 = H) and **143a,b** also showed good activity compared to AA **5** [83].

From these two compounds **144a,b** (Fig. 18), the former **144a** showed significant antioxidant activity in the ABTS method, using AA **5** as standard, and protected the DNA from damage in the Bleomycin-dependent DNA damage assay. Another derivative, compound **145** (Fig. 18), also exhibited significant antioxidant activity and protected the DNA from damage [84].

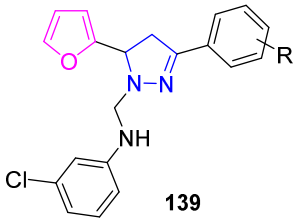
Among thiophene-pyrazole conjugates **146a-l** (Fig. 18), compounds **146c**,**d**,**g**,**i**, having fluoro, chloro, methyl and methoxy substitutions at *para*-positions of the benzene ring

exhibited excellent DPPH RSA in comparison with AA **5**. Compounds **146a**,**b**,**e**,**f**,**h**,**l** showed moderate activity while the compounds **146j**,**k** having nitro substitution showed weak antioxidant activity probably due to the stronger electron withdrawing effect of the nitro group [85].

Among pyrazolines carrying an arylfuran/arylthiophene moiety **147a-n** (Fig. 18), compounds **147a**,**f**,**h**,**o** showed significant antioxidant activity when compared with BHT **7,** using the DPPH method [86]. Compounds **147a**,**h** with a methyl substituent at the *para*-position of the phenyl ring showed good activity compared to BHT **7**, while **147f**,**o** with a nitro substituent at the *para*- and *meta*-positions, respectively, exhibited moderate activity. The compound bearing a furan moiety **147a** showed the highest activity towards the $DPPH^{\bullet}$ radical.

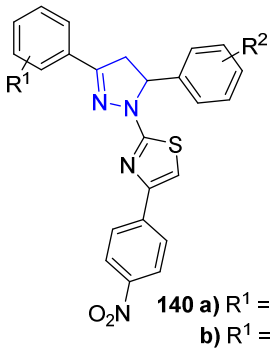


138

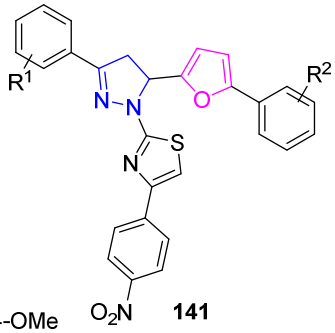


139

a) R = H, **b)** R = 4-Cl, **c)** R = 4-Br, **d)** R = 2-OH, **e)** R = 4-OH

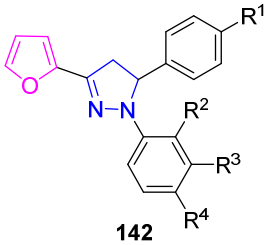


140 **a)** R^1 = 4-SMe, R^2 = 4-OMe
b) R^1 = 4-SMe, R^2 = 3,4-$(OMe)_2$
c) R^1 = 4-SMe, R^2 = 4-NO_2
d) R^1 = 4-SMe, R^2 = 4-Cl
e) R^1 = 4-SMe, R^2 = 2,4-Cl_2



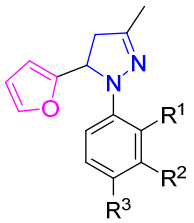
141

a) R^1 = 2,4-Cl_2; R^2 = 3,4-$(OMe)_2$
b) R^1 = 3-Cl, 4-F; R^2 = 3,4-$(OMe)_2$
c) R^1 = 2,4,5-Cl_3; R^2 = 3,4-$(OMe)_2$
d) R^1 = 4-NO_2; R^2 = 3,4-$(OMe)_2$
e) R^1 = 2-Me, 4-NO_2; R^2 = 3,4-$(OMe)_2$
f) R^1 = 4-Cl; R^2 = 3,4-$(OMe)_2$
g) R^1 = 2-Me, 6-NO_2; R^2 = 3,4-$(OMe)_2$
h) R^1 = 4-OMe, 2-NO_2; R^2 = 3,4-$(OMe)_2$
i) R^1 = 4-Br; R^2 = 3,4-$(OMe)_2$
j) R^1 = 4-Cl, 2-NO_2; R^2 = 3,4-$(OMe)_2$
k) R^1 = 4-Cl, R^2 = H



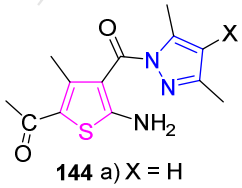
142

a) R^1 = H, R^2 = H, R^3 = Me, R^4 = H; **b)** R^1 = H, R^2 = Me, R^3 = H, R^4 = Me
c) R^1 = F, R^2 = H, R^3 = Me, R^4 = H; **d)** R^1 = F, R^2 = Me, R^3 = H, R^4 = Me
e) R^1 = Me, R^2 = H, R^3 = Me, R^4 = H; **f)** R^1 = Me, R^2 = Me, R^3 = H, R^4 = Me
g) R^1 = OMe, R^2 = H, R^3 = Me, R^4 = H; **h)** R^1 = OMe, R^2 = Me, R^3 = H, R^4 = Me
i) R^1 = Cl, R^2 = Me, R^3 = H, R^4 = Me; **j)** R^1 = Cl, R^2 = Me, R^3 = Me, R^4 =Me

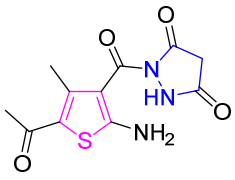


143

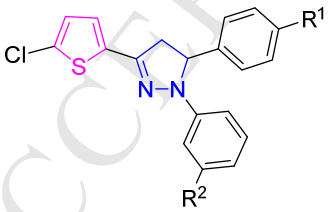
a) R^1 = H, R^2 = Me, R^3 = H
b) R^1 = Me, R^2 = H, R^3 = Me
c) R^1 = H, R^2 = H, R^3 = H



144 a) X = H
b) X = Cl

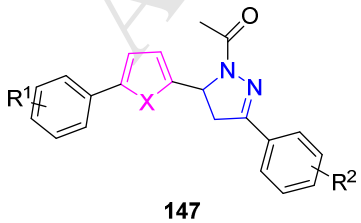


145



146

a) R^1 = R^2 = H;
b) R^1 = F, R^2 = H;
c) R^1 = F, R^2 = Cl;
d) R^1 = Cl, R^2 = H;
e) R^1 = R^2 = Cl;
f) R^1 = Me, R^2 = H;
g) R^1 = Me, R^2 = Cl
h) R^1 =OMe, R^2 = H
i) R^1 = OMe, R^2 = Cl
j) R^1 = NO_2, R^2 = H
k) R^1 = NO_2, R^2 = Cl
l) R^1 = $N(Me)_2$, R^2 = H



147

a) R^1 = 4-NO_2, R^2 = 4-Me, X = O; **b)** R^1 = 4-NO_2, R^2 = 4-Me, X = O
c) R^1 = 4-NO_2, R^2 = 4-Cl, X = O; **d)** R^1 = 4-NO_2, R^2 = 2,4-Cl, X = O
e) R^1 = 4-NO_2, R^2 = 4-OH, X = O; **f)** R^1 = 4-NO_2, R^2 = 4-NO_2, X = O
g) R^1 = 4-NO_2, R^2 = 4-NH_2, X = O; **h)** R^1 = 2-NO_2, R^2 = 4-Me, X = O
i) R^1 = 4-NO_2, R^2 = 4-Me, X = S; **j)** R^1 = 4-NO_2, R^2 = 4-OMe, X = S
k) R^1 = 4-NO_2, R^2 = 4-Cl, X = S; **l)** R^1 = 4-NO_2, R^2 = 2,4-Cl, X = S
m) R^1 = 4-NO_2, R^2 = 4-NO_2, X = S; **n)** R^1 = 4-NO_2, R^2 = 3-NO_2, X = S

Fig. 18. Pyrazole derivatives containing furan and thiophene moieties **138-147** [81,82,83,84,85,86].

2.1.15. Benzofuran conjugated pyrazoles

Among benzofuran based 1,3,5-trisubstituted dihydropyrazoles **148a-o** and **149a-o** (Fig. 19), compounds **148g**,**h**,**k**,**m** and **149g**,**h**,**k**,**m** showed excellent antioxidant activity as compared with AA **5** [87,88]. Other benzofuran based dihydropyrazoles **150** and **151** (Fig. 19) exhibited considerable DPPH RSA, probably due to the presence of hydroxy and electron-donating methoxy group at 5-substituted phenyl ring and also the presence of the NH group in compound **150** [89]. However the coupling of **151** with substituted anilines afforded a series of benzofuran based 1,3,5-trisubstituted pyrazole analogues **152a–l** with significant increase of the antioxidant activity. Dominant RSA was found for derivatives **152d**,**f**, which exhibited good antioxidant properties higher than that of BHA **8** in DPPH and inhibition of microsomal lipid peroxidation in *in vitro* assays. These compounds were 10 to 13-folds more active compared to the benzofuran scaffolds **150** and **151** in DPPH assay [89]. This may be due to the presence of hydroxy and methoxy groups at 5-substituted phenyl ring and also the presence of these groups in the 1-substituted carboxamide phenyl ring. Contrarily, the presence of EWG (Br, Cl, NO_2 and F) in the carboxamide phenyl ring of **152g**,**h**,**k**,**l** is not favourable to enhance the antioxidant activity. The other compounds **152b**,**c**,**e**,**i**,**j** that contain electron-donating single hydroxy, methoxy and methyl groups at positions 3-,4- and 5- exhibited significantly higher RSA activity than that of **150** and **151**. Since compound **152a** does not have any substituent on the ring it showed least activity compared to other compounds. Thus, the antioxidant activity of these compounds is related with their electron- or hydrogen-donating ability to $DPPH^{\bullet}$ radical so that it becomes stable diamagnetic molecules.

Benzofuranyl-pyrazoles **153**, **154**, **155** (Fig. 19) showed moderate antioxidant activity by ABTS method. The IC_{50} values (**153**, 95.51 ± 1.62 µM; **154**, 89.94 ± 1.59 µM; **155**, 70.83 ± 1.32 µM) were significantly different ($p<0.05$) from that of AA **5** that showed potent ability to inhibit free radicals with IC_{50} values of 12.10±0.51 µM [90].

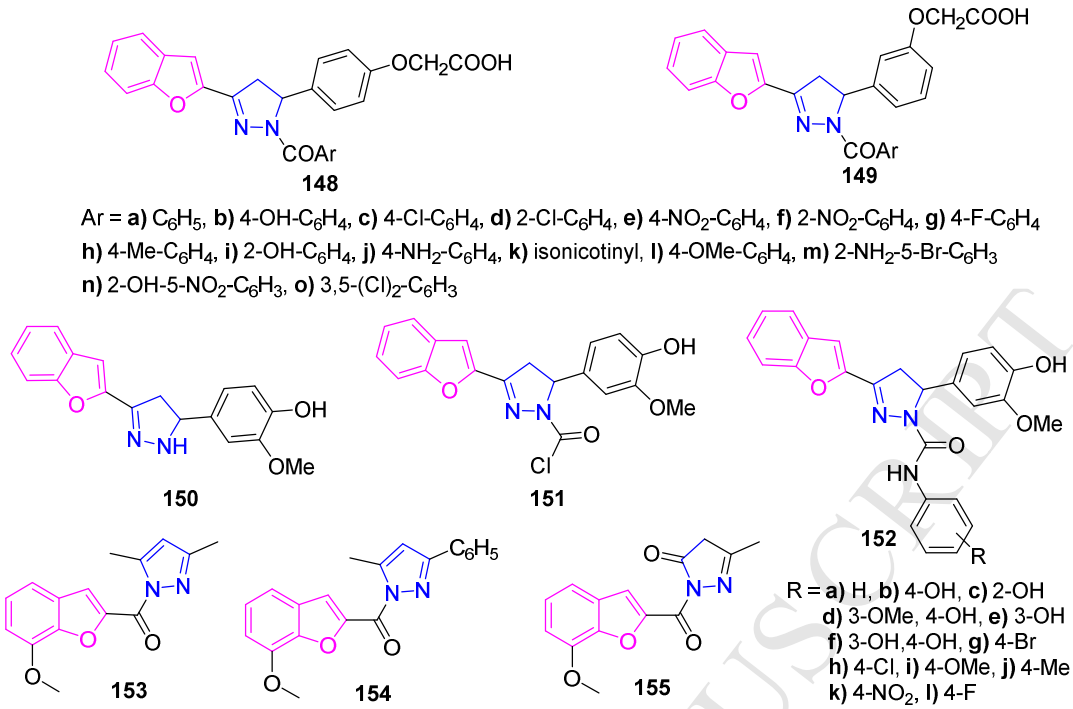


Fig. 19. Benzofuran-based pyrazole derivatives **148-155** [87,88,89,90].

2.1.16. Pyrano[2,3-c]pyrazoles and thieno[2,3-c]pyrazoles

2,5-Disubstituted indoles containing a pyrano[2,3-*c*]pyrazole moiety **156a-e** (Fig. 20) exhibited good RSA, however none of them was better than the standard compounds, BHA **8** and TBHQ **17**, using DPPH method [91]. At a concentration of 80 µg/mL compounds **156a** (IC_{50} 19.60 µg/mL), **156d** (IC_{50} 12.59 µg/mL) and **156e** (IC_{50} 13.19 µg/mL) exhibited 76.65, 76.10 and 70.20 % RSA, respectively. At 60 µg/mL compounds **156d** and **156e** were still active with 76.10 and 74.50 % RSA, respectively and compound **156d** exhibited highest RSA 80.10% and 79.60 % at 20 and 40 µg/mL, respectively. Compounds **156b** (IC_{50} 14.93 µg/mL) and **156e** (IC_{50} 13.19 µg/mL) were less active with RSA in the range 66.57–76.10 % at 20 and 40 µg/mL, respectively. The RSA of compounds **156a-e** may be due to the presence of pyrano[2,3-*c*]pyrazole unit and isonicotyl groups at 3-position of the indole nucleus. These groups may help to stabilize the free radical formed after transfer of an electron or hydrogen to the stable $DPPH^{\bullet}$ radical [91].

The syringyl substituted dihydro-pyrano[2,3-*c*]pyrazoles **157a**,**d**,**g**,**j** and **158a**,**d**,**g** (Fig. 20) have shown excellent RSA in DPPH and ABTS methods proving to have much better antioxidant activity than trolox **10** [92]. SAR studies showed that the introduction of methoxy substituent in aromatic groups of these dihydro-pyrano[2,3-*c*]pyrazoles could significantly increase their RSA and the substituted moieties at N or C-3 position

could potentially influence on their antioxidant activity. For example, dihydro-pyrano[2,3-*c*]pyrazoles with a methyl or phenyl at C-3 position presented better scavenging rate than dihydro-pyrano[2,3-*c*]pyrazoles with ethyl or *tert*-butyl, due to the relatively weak electron-donating ability of methyl and phenyl groups comparing with ethyl and *tert*-butyl groups. In addition the phenyl group can form great conjugated π bond system with pyrano[2,3-*c*]pyrazole explaining the better antioxidant activity of this derivative. Furthermore, when N atom is linked with H atom, free H atom reacting with free radical can promote the scavenging rate of 2*H*,4*H*-dihydro-pyrano[2,3-*c*]pyrazoles **157**, while N-1 atom linked with Ph group of 1*H*,4*H*-dihydro-pyrano[2,3-*c*]pyrazoles **158**, the phenyl group forming great conjugated system with pyrano[2,3-*c*]pyrazole, is advantageous to stabilize free radicals thus promoting the reaction. So, both dihydro-pyrano[2,3-*c*]pyrazoles **157** and **158** exhibited excellent free radicals elimination rate [92].

Pyrano[2,3-*c*]pyrazoles **159a-o** (Fig. 20) showed high antioxidant activity when compared with both α-tocopherol **6** and AA **5** at 125–4000 μg/mL in the ABTS assay [93]; with IC_{50} values in the range of 104–3133 μM. Compounds **159o**,**n**,**a**,**e**,**h** were much more active than AA **5** and **159o**,**n**,**a** were much more active than α-tocopherol **6**. Compound **159l** showed weaker activity than both α-tocopherol **6** and AA **5**. The high antioxidant activity of bisproduct **159o** was related to the extended conjugated system, which can stabilize the free radical via resonance through a longer conjugated system.

2,4-Dihydropyrano[2,3-*c*]pyrazoles bearing H (**160a**), EDGs (**160b-g**), EWGs (**160h-p**) at different positions of the aromatic ring and heterocyclic moieties at the C-4 position (**160q–t**) presented antioxidant and neuroprotective activity (Fig. 20) [94]. A combination of rotenone (30 μ M) and oligomycin A (10 μ M) (R/O) was used to induce neurotoxicity as a model system to evaluate the potential neuroprotective activity of the compounds. Melatonin **20**, a well-known antioxidant natural compound, was included as a positive control. Compounds **160a-t** exhibited interesting antioxidant neuroprotective activities and almost all derivatives showed greater neuroprotective effect than melatonin **20**. The antioxidant neuroprotective effect depends not only on the type of substituents but also on its position on the aromatic ring, increasing from *ortho*- to *para*- and *meta*-derivatives. The 3-pyridyl analogue was found to be the best neuroprotectant agent against the R/O combination being able to reduce 57.9% of cell death.

From a series of benzopyran-annulated pyrano[2,3-*c*]pyrazoles, compounds **161a** and **161b** (Fig. 20) have demonstrated high ferric reducing antioxidant capability (330-340 mM/100 g) [95].

A series of spiro[indoline3,4'-pyrano[2,3-*c*]pyrazole] derivatives **162a-l** (Fig. 20) showed potent FRSA against DPPH$^{\bullet}$ and NO$^{\bullet}$ radicals and moderate FRSA against ABTS$^{+\bullet}$ radical when compared with AA **5** [96]. Among these compounds, **162a,f**

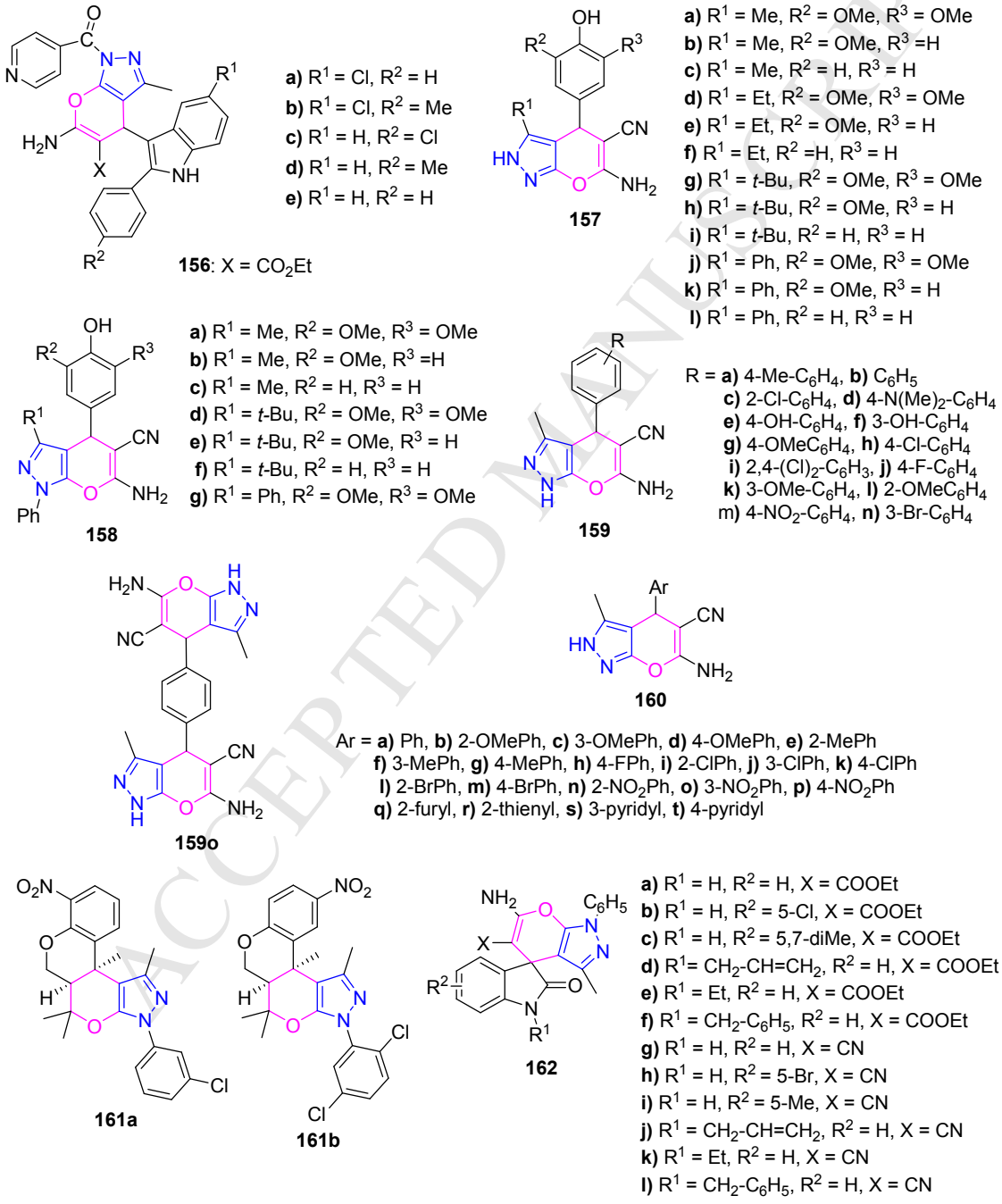


Fig. 20. Pyrano[2,3-*c*]pyrazoles **156-160,** benzopyran-annulated pyrano[2,3-*c*]pyrazoles **161**

and spiro[indoline3,4'-pyrano[2,3-*c*]pyrazole] derivatives **162** [91,92,93,94,95,**Error! Bookmark not defined.**].

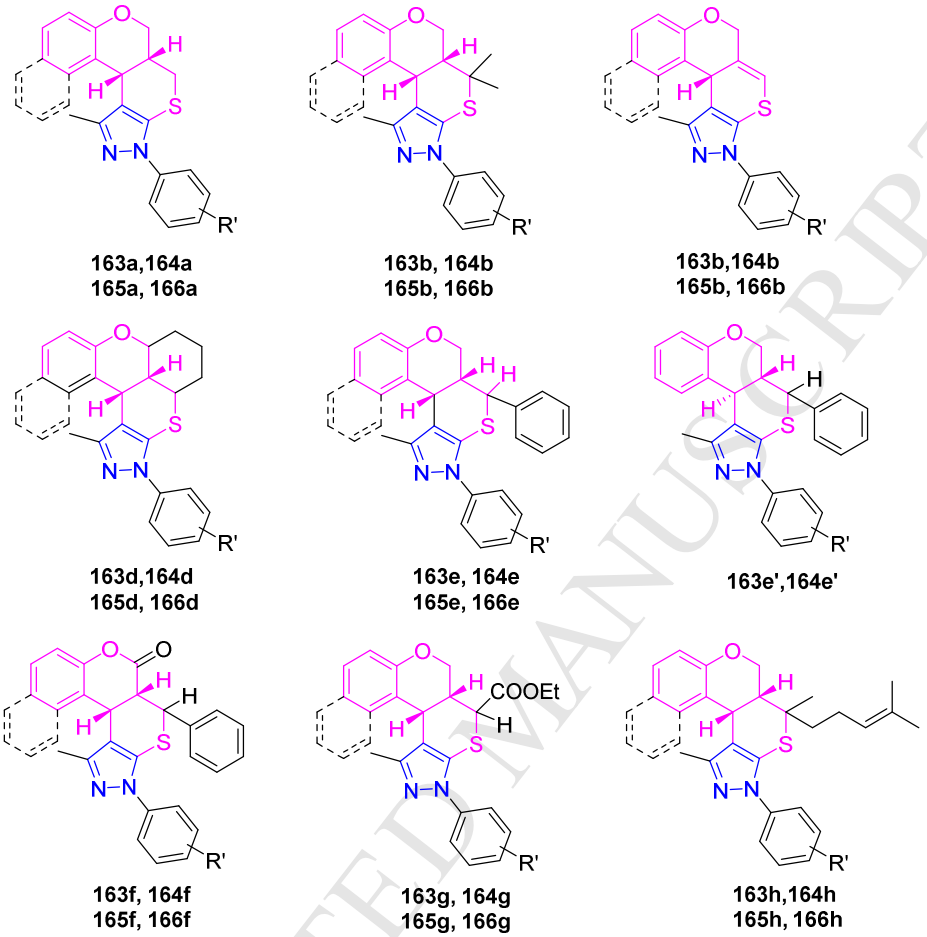
showed highest activity and a correlation between substitution in indole ring and substitution at 5-position of the pyran ring was observed [**Error! Bookmark not defined.**]. In general, the presence of EDGs, in both the indole and the pyran rings, enhanced the FRSA.

The antioxidant activity of new chromeno-annulated thiopyrano[2,3-*c*]pyrazoles **163-166** (Fig. 21) was screened by determining FRAP values at a concentration of 200 μg/mL in comparison with AA **5** at 176 μg/mL [97]. The results found were in the range 220-300 mmol/100 g, indicating good antioxidant potential of these compounds.
The role of thieno[2,3-*c*]pyrazoles as antioxidants was tested against toxicity caused by 3-nonylphenol, a chemical pollutant, on the red blood cells of Nile fishes, specifically African catfishes (*Clarias gariepinus*) [98]. Although, all the thienopyrazoles **167a-f**, **168a-f** and **169** (Fig. 21) were found to be active and non-cytotoxic, those bearing a 4-aminocarboxamide **168b** showed a potent antioxidant potential, followed by compound **168f,** against 4-nonylphenol toxicity. An improvement in red blood cells morphology appeared in the group of fish treated with 4-nonylphenol in combination with compound **168b** and the group treated with 4-nonylphenol in combination with compound **168f** compared to the treated fishes with 4-nonylphenol only. Compound **169** also showed antioxidant role but was less active than the other compounds.

2.1.17. Oxodiazole linked pyrazoles

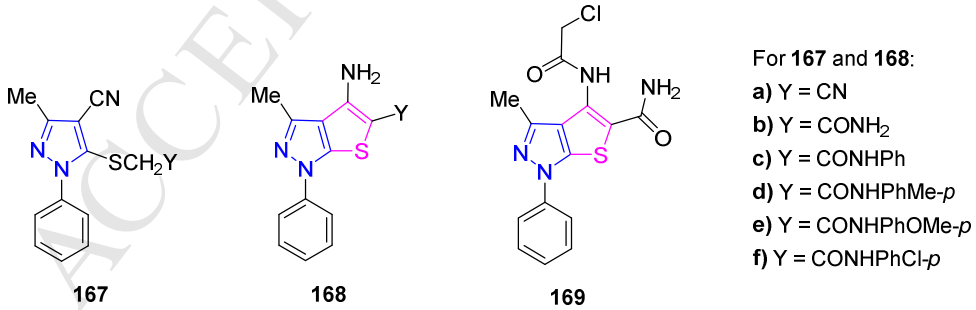
Of all the pyrazoline amidoximes **170a–d** and pyrazolyl-1,2,4-oxadiazoles **171a–p** and **172** (Fig. 22) [99], the compounds **171f**,**h**,**o**,**p** showed good interaction with DPPH$^{\bullet}$ radical in the order (**171o** >**171h** >**171p** >**171f**). The higher antioxidant activity of these compounds seems to be related with their electron or hydrogen donating ability to DPPH$^{\bullet}$ radical, so that they become stable diamagnetic molecules. It is noteworthy that compound **171o** showed more promising DPPH RSA than AA **5** probably due to the presence of three methoxy and one hydroxy groups on benzene rings. Compound **170d** with only one hydroxy group on benzene ring showed propitious DPPH RSA. The presence of free $-NH_2$ and –OH group in the amidoximes **170a–d** might add on to the electron donating capacity to DPPH$^{\bullet}$ radical thus increasing activity. Compound **171f** showed the more potent reducing power activity, probably due to the presence of two

halogen atoms on benzene rings. Compound **170a** showed 3 fold enhanced lipid peroxidation inhibitory activity than α-tocopherol **6** at 10 μg/mL concentration that may be due to the ability of amidoximes to donate NO under mild oxidants. NO can serve as



R' = 4-Me (**163a-h**); 3-Cl (**164a-h**), obtained from the reaction of pyrazole 5-thiones with salicylaldehyde-substrates

R' = 3-Cl (**165a-h**); R ' = H (**166a-h**), obtained from the reaction of pyrazole 5-thiones with naphthaldehyde-substrates



For **167** and **168**:
a) Y = CN
b) Y = $CONH_2$
c) Y = CONHPh
d) Y = CONHPhMe-*p*
e) Y = CONHPhOMe-*p*
f) Y = CONHPhCl-*p*

Fig. 21. Chromeno-annulated thiopyrano[2,3-*c*]pyrazoles **163-166**, thienopyrazole **167** and thieno[2,3-*c*]pyrazoles **168-169** [97,98].

a chain-terminating antioxidant and reduces oxidative injury to mammalian cells by attenuation of metal/peroxide oxidative chemistry, as well as lipid peroxidation.

Compounds **173** and **174** showed excellent antioxidant activity in the ABTS assay and high protection against DNA damage induced by the Bleomycin iron complex (Fig. 22) [100]. The high antioxidant activity of these compounds may be attributed to the presence of a hydroxy group attached to an aromatic ring in **174** or the secondary amino group in **173** that can act as scavenging of free radicals. Other compounds **175-178** showed only moderate activity. The presence of pyrazole or pyrazolopyrimidine moieties at the 5-position of the 1,3,4-oxadiazole ring enhanced the antioxidant activity while other groups such as tetrahydrobenzothiophene or pyrano[2,3-*c*]pyrazole have an opposite effect.

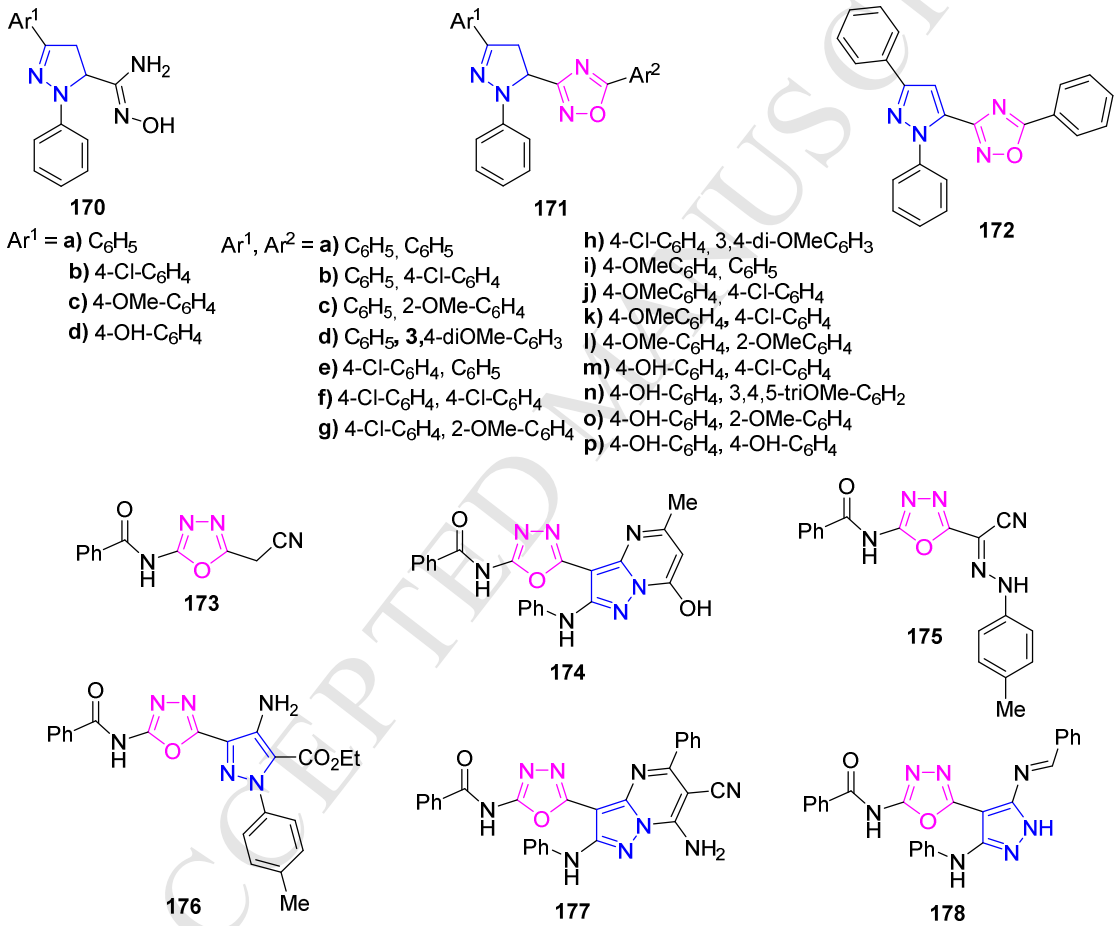


Fig. 22. Pyrazoline amidoxime **170**, pyrazolyl-1,2,4-oxadiazoles and 2-benzoylamino-5-hetaryl-1,3,4-oxadiazoles **171-178** [99,100].

2.1.18. Pyrazole-derivatized indoles

Eight indolopyrazolines were found to be good at scavenging DPPH$^{\bullet}$ and ABTS$^{+\bullet}$ radicals when compared with AA **5** at the same concentrations. However, regarding IC_{50} values, compounds **179c** and **180c,d** (Fig. 23) were the best compounds in scavenging both free radicals with IC_{50} comparable to that of the AA **5** [101].

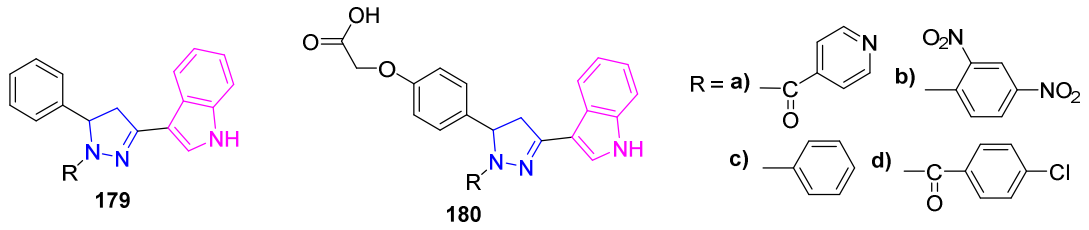
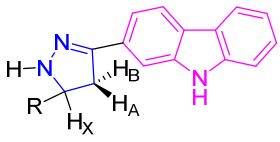


Fig. 23. Indolo-2-pyrazoline derivatives **179-180** [101].

2.1.19. Pyrazole-derivatized carbazoles

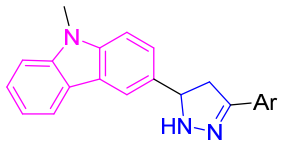
A series of pyrazolines derivatized with carbazole (Fig. 24), containing nitro (**181e**), styryl (**181h**) and methoxy (**181j**) groups, showed very good activity, in the FRAP assay, compared to BHA **8**. The antioxidant activity seems to be related with their redox properties, which allow them to act as reducing agents or hydrogen-atom donors, their ability to chelate metals, inhibit lipoxygenase and scavenge free radicals. These compounds function as free-radical scavengers and chain breakers, complexes of pro-oxidant metal ions and quenchers of singlet-oxygen formation. The other derivatives **181b**,**c**,**d**,**f**,**g** with chloro- and hydroxyl-substituents shown moderate activity while **181a**,**i**,**k** with phenyl, methyl and *p*-tolyl groups, respectively, have shown least activity compared to BHA **8** [102].

At 100 µM concentration, all the carbazole-pyrazoline conjugates **182a–o** (Fig. 24) exhibited good DPPH$^{\bullet}$ (72.01-92.08%) and $^{\bullet}O_2^-$ radical (SOR) scavenging activity (45.65-86.26%), compared to AA **5** (91.52% and 51.95 % for DPPH and SOR, respectively) [103]. Compounds **182c** (69.34%), **182d** (74.34%), **182i** (69.34%) and **182k** (78.64%) exhibited good hydroxyl RSA when compared to AA **5** (88.34%) while the rest of the compounds have shown moderate hydroxyl RSA. SAR studies revealed that dihalogenated compounds show higher superoxide RSA that the monohalogenated ones. Those with heteroaromatic ring, such as thiophene **182n** (63.15%), shows similar superoxide RSA to that of **182a** with unsubstituted aromatic ring (63.45%), while the one with pyridine ring **182o** (54.84%) shows lower activity than **182a**. In general, disubstituted compounds showed higher hydroxyl RSA than the monosubstituted compounds.



181

R = **a)** C_6H_5-, **b)** 2-Cl-C_6H_4-, **c)** 3-Cl-C_6H_4-, **d)** 4-Cl-C_6H_4-
e) 4-NO_2-C_6H_4-, **f)** 2-OH-C_6H_4-, **g)** 4-OH-C_6H_4-
h) styryl, **i)** Me, **j)** *p*-anisyl, **k)** 4-Me-C_6H_4-



182

Ar = **a)** C_6H_5-, **b)** 4-OMe-C_6H_4-, **c)** 3,4-$(OMe)_2$-C_6H_3-
d) 1,3,5-$(OMe)_3$-C_6H_2-, **e)** 4-F-C_6H_5-
f) 2,4-$(F)_2$-C_6H_3-, **g)** 3,4-$(F)_2$-C_6H_3-, **h)** 4-Cl-C_6H_4-
i) 2,4-$(Cl)_2$-C_6H_3-, **j)** 3,4-$(Cl)_2$-C_6H_3-,
k) 2,5-$(Cl)_2$-C_6H_3-, **l)** 4-Br-C_6H_3-, **m)** 4-NO_2-C_6H_4-
n) tiophen-2-yl-, **o)** pyridin-2-yl-

Fig. 24. 2-Pyrazoline derivatized carbazoles **181-182** [102,103].

2.1.20. Pyrazole derivatives incorporating quinoline/isoquinoline scaffolds

The pyrazolo[4,3-*c*]quinolines **183a-i** and **184a-b** (Fig. 25) showed weak to moderate RSA using DPPH method with respect to AA **5**. However, methoxy substituted compounds **183e**,**g**,**h** showed significant scavenging activity, probably due to the presence of the EDG at the *para*-position of the phenyl ring, which may enhance the stabilization of the resulting oxygen radical. Moreover, compound **183g** showed significant reducing antioxidant power compared to BHT **7** that may be attributed to the presence of the chloro substituent at C-6 of the quinolone ring. Total antioxidant assay was carried out for all the compounds, however they did not show total antioxidant activities as effective as AA **5**, with exception of compounds **183a** and **183c** that showed mild activity [104].

Some indolo[2,3-*c*]isoquinolinyl pyrazole derivatives **185b**,**c**, **186b**,**c** and **187a**,**b** (Fig. 25) presented good RSA compared with standards, AA **5**, BHA **8** and TBHQ **17** [105]. The most active compounds were those bearing chloro and methoxy groups as substituents.

The DPPH RSA of imidazoquinoline carrying chalcone and pyrazoline moieties **188a-d**, **189a-d** and **190a-d** (Fig. 25) was found to be concentration-dependent, increasing with the increase of the concentration [106]. All the compounds showed moderate antioxidant activity with slight variation, with exception of compounds **188a**,**d** and **189d** that have shown excellent DPPH RSA (82.13–71.10 %) as compared to AA **5** (78.20 %), being the most effective antioxidants. According to these results the steric hindrance and the additional electron cloud on the core molecule hinders the free radicals. The derivatives with EDGs (OMe) on the phenyl ring of chalcones and

pyrazolines, which induce the resonance and stabilize the molecules, have high antioxidant activity while those having EWGs (Cl and NO_2) do not facilitate free radical hindrance and reduce the ability of hydrogen discharge from the amino group of pyrazolines. The modification of the chalcone into the pyrazoline moiety did not cause significant loss of antioxidant activity.

A series of isoquinolinyl-substituted pyrazoles **191a-h** (Fig. 25) had good antioxidant activity in DPPH assay in comparison with BHT **7** [107].

Excellent RSA was found for dihydropyrazole **192e** (IC_{50} = 21.0 ± 0.7µg/mL) by DPPH method compared to AA **5** (IC_{50} = 48.7 ± 0.2µg/mL) and BHT **7** (IC_{50} = 61.3 ± 0.5µg/mL), while compounds **192c** (IC_{50} = 34.5 ± 0.5µg/mL), **192d** (IC_{50} = 27.3 ± 1.2µg/mL), **192f** (IC_{50} = 28.3 ± 0.6µg/mL) and **192g** (IC_{50} = 31.3 ± 1.4µg/mL) showed less activity than **192e** but better than AA **5** and BHT **7** (Fig. 25) [108]. The hydroxy substituent present in the phenyl ring is considered one of the key groups to enhance greatly the antioxidant activity due to its easy conversion to phenoxy radicals via HAT mechanism. In addition, the presence of methoxy substituent also increases the DPPH

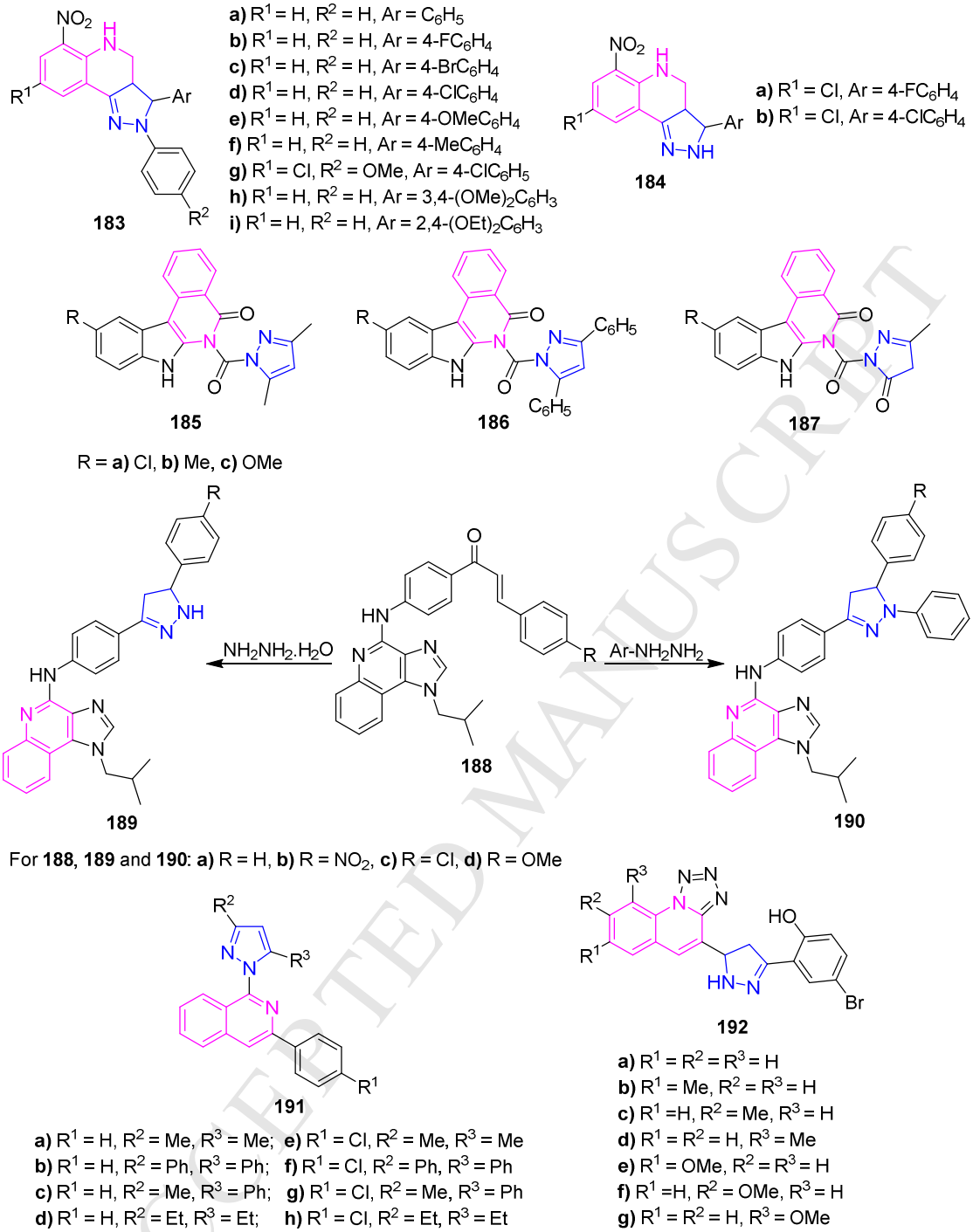


Fig. 25. Pyrazole derivatives incorporating quinoline/isoquinoline scaffolds **183-192** [104,105,106,107,108].

RSA. The ADMET parameters found for these compounds showed good drug-like properties including good oral bioavailability and good intestinal availability.

2.1.21. Pyrazolyl-substituted quinoxalines and quinoxaline-1,4-di-N-oxides

The antioxidant ability of 4,5-dihydro-(1*H*)-pyrazole analogues of **193** (Fig. 26) was tested in comparison to well-known antioxidant agents, nordihydroguaiaretic acid (NDGA) **19**, a natural compound used as a nutritional supplement, trolox **10**, and caffeic acid **18** [109]. The insertion of a dihydropyrazolyl ring increases the DPPH RSA (for compounds **194a**,**b**) when compared to the precursor compounds (**194a** is much more active than **193a**); being compound **194b** (R = F) more active than **194a**. All tested compounds demonstrated hydroxyl RSA higher than trolox **10**, however lipophilicity is not well correlated with the results. On the other hand, the majority of the compounds does not present superoxide anion RSA at 0.1 mM, with the exception of compound **193a** (100%) which is the most potent.

The antioxidant activity of quinoxalines and quinoxaline-1,4-di-*N*-oxides **195-198** was evaluated by several different assays to study a broader spectrum of scavenging properties in comparison with NDGA **19**, trolox **10**, and caffeic acid **18**. The most active derivatives where those with the pyrazoline moiety (series **195**, **196** and **198**) (Fig. 26) [110]. In particular, those derivatives bearing a quinoxaline-*N*-oxide moiety (series **195** and **198**) presented increased antioxidant activity compared to analogues of series **196**. In the DPPH assay, compounds **195c**,**e**,**f**, **196c**,**f** and **198a**, showed the higher RSA, some of them displaying similar interaction percentage (70-72%) to that of NDGA **19** (83%) at the same concentration. These compounds are able to donate a hydrogen atom due to the presence of a phenolic group or a free amino pyrazoline ring in their structure. In addition, the presence of *N*-oxide groups in compounds of series **195** and **198** might increase the hydrogen donation ability of the amino group, facilitating the release of this atom and increasing the scavenging activity. The presence of both NH and OH groups in the same molecule (such as in **198a**) seemed to increase its antioxidant activity. These compounds also possessed the best activities in the ABTS assay but an opposite trend was observed; in this assay, compounds **196c**,**f** were more active than **195c**,**e**,**f**. Most of these compounds are good $^{\bullet}$OH radical scavengers when compared to trolox **10**, however they did not exhibit significant superoxide RSA. Compounds **197b**,**d**, with a free amino group in their structure, presented a good lipid peroxidation inhibition activity, especially the derivative with a hydrogen atom in R^2 position **197a**, of the quinoxaline ring. Replacement of the hydrogen by a fluoro atom led to a decrease of the activity; however, the fluorinated derivatives showed also significant values of lipid peroxidation inhibition.

Some phenylpyrazolo indoquinoxalines **199a-o** (Fig. 26), have shown significant antioxidant activity at a concentration of 10 µg/mL; among them compounds **199c** 45.45%, **199e** 50.49%, **199m** 40.59%, **199n** 58.33% and **199o** 59.40% presented good FRSA when compared with AA **5** at the same concentration (40.00%) [111]. The presence of substituents like methoxy, fluoro or chloro in the phenyl ring, at position 5 of pyrazoline seems important for the RSA, since non-substituted compounds or those having a hydroxy group at that position were less active.

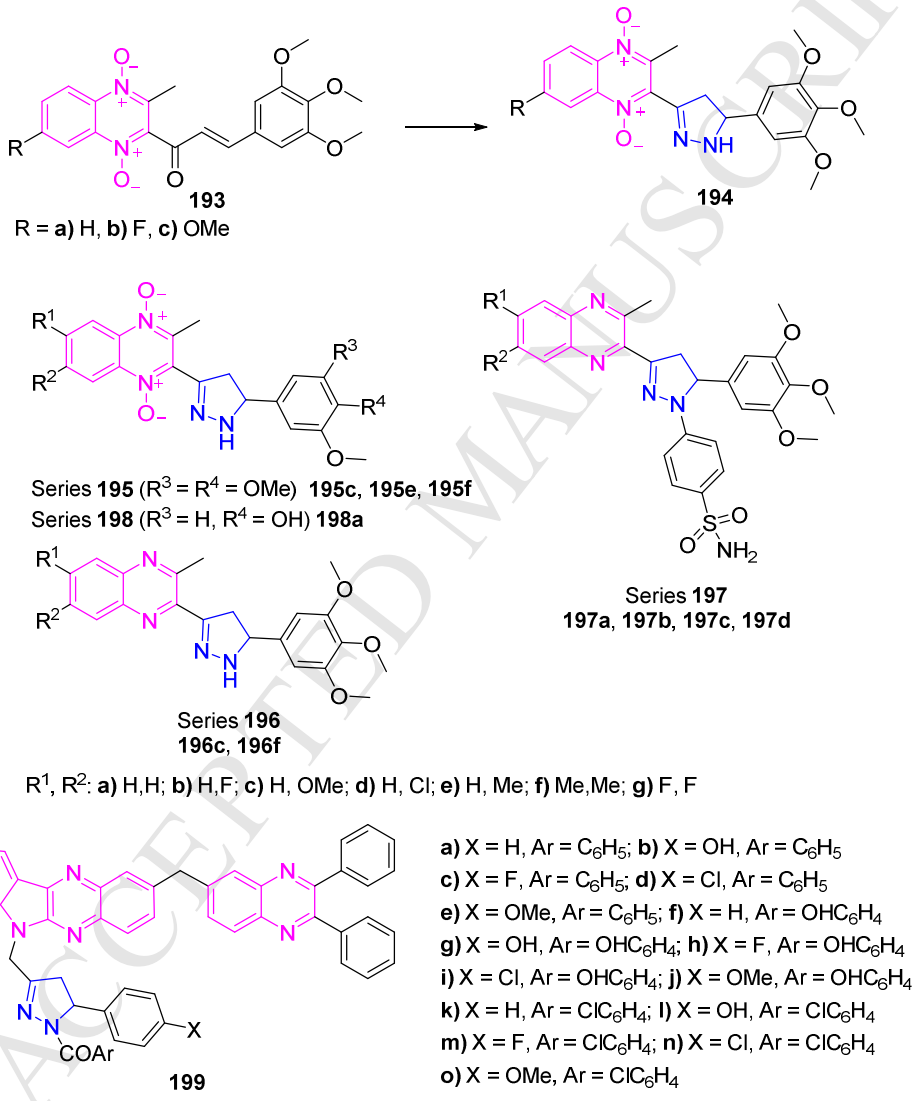


Fig. 26. Pyrazolyl-substituted quinoxaline and quinoxaline-1,4-di-*N*-oxides **193-198** and phenylpyrazolo indoquinoxalines **199** [109,110,111].

2.1.22. Pyridyl/pyrimidyl-conjugated pyrazole derivatives

Among 1,4-dihydropyridines containing substituted pyrazole moieties **200a-l** (Fig. 27), compounds **200c**,**e**,**f** showed significant DPPH RSA (> 60%) whereas the others showed weak scavenging activity (25.3-35.2%) as compared to BHT **7** (74.4%) [112]. In acute oral toxicity tests, compounds **200c**,**e** were safe up to 3000 mg/kg, however mortality was found for compound **200f** in above 2000 mg and experimental animals showed significant alterations in their behaviour. The increase of the chain length of the ester moieties at C-3 and C-5 led to a higher antioxidant activity. Among the most potent compounds **200c**,**e**,**f**, those having chlorine atoms in the substituent **200c** (61.1%) and **200f** (62.3 %) were slightly less potent than 4-anisyl substituted compound **200e** (65.3%) [112].

All the pyrazolines bearing a pyridyl moiety **201a-i** (Fig. 27) showed good antioxidant activity, by DPPH method, with small variations depending on the substitution on phenyl ring, but were much less active than AA **5** (96.67 % inhibition at 25µg/ml) [113]. The percentage inhibition was found to be concentration-dependent, increasing with the increase of compound's concentration. Compound **201h** (60.19 % inhibition at 125µg/ml) showed higher antioxidant activity compared with the other derivatives (26.23-59.87% inhibition at 125 µg/ml) probably due to the strong electron-donating effect of the substituent on *para*-position of phenyl ring. These compounds also showed drug-like properties and good bioavailability.

At a concentration of 100 µg/mL the pyridylpyrazole **202** (Fig. 27) with a hydroxyl-functionalised arm exhibithed a RSA of about 73%. Regarding the IC_{50} values, the results showed moderate antioxidant activity for compound **202** (31.8 µg/ml) when compared to AA **5** (2.82 µg/ml) and BHA **8** (6.8 µg/ml). This activity should probably be attributed to the high radical scavenging property of the hydroxy substituent [114].

The FRAP assay of 5-imidazopyrazole incorporated 2-amino-3-cianopyridine **204a-f**,**i**,**k**, **205a**,**d-f** (Fig. 27) was found to range from 401.22 to 497.10 mmol/100 g indicating that the compounds are excellent antioxidants when compared with AA **5** [115]. The remaining compounds exhibited moderate antioxidant activity with exception of **204g**,**h** that presented weak antioxidant activity. The most active compound was **204c**. The effect of substituting H by Me was found to increase the antioxidant activity since **204l** was 2 times more potent than **204k** and **205d** was 2 times more potent than **205c**. The compounds with electron donating phenyl group at C-6 of the pyridine ring possessed superior inhibition than compounds with electron

withdrawing and other heterocyclic groups. Among the compounds with heterocyclic substitution, compounds **205e**,**f** were more active than the other derivatives of this series probably due to the presence of the coumaryl unit since coumarins are known to have antioxidant activity [115].

Among pyrazoles **206a-j** (Fig. 27), some derivatives have shown moderate to good antioxidant activity, by scavenging of hydrogen peroxide, $NO^{\bullet}$ radical, lipid peroxidation inhibition and reducing power determination, but in general it was lower than that of AA **5** [116]. Compound **206j** was found to be the most active, in all the methods, probably due to the presence of two hydroxy groups in adjacent positions.

Pyrazole containing pyrimidines **207a-f**, 1,4-dihydropyridines **208a-f**, and imidazole derivatives **209a,b** (Fig. 27) showed promising DPPH FRSA, however dihydropyrimidinones **207c** (89.41 %) and **207f** (83.34 %) exhibited excellent DPPH RSA as compared to GSH (89.09 %) [117]. The antioxidant activity of these compounds is due to the acidic proton in the pyrimidinone ring and the presence of the other groups as substituents. In the dihydropyridine series **208a-f**, acetyl substituted **208c**,**f** have better RSA compared to ester-substituted derivatives **208a**,**b**,**d**,**e**, probably due to the rapid keto-enol tautomerism presented by these compounds. Imidazole substituted compounds **209a**,**b** were less active than **207a-f** and **208a-f**. Moreover, compounds **207a**,**b**,**e** and **208a** showed good reducing power capacity while **207c**,**d**, **208c**,**f** and **209b** exhibited moderate reducing power capacity in comparison with the standard GSH.

2.1.23. Pyrazolopyridines, pyrazolopyrimidines and pyrazolopyrimidin-4-ones

The antioxidant activity of pyrazolopyridines **210** and **211**, determined by ABTS assay, was found to be the highest, compared with AA **5**, whereas compounds **212**, **213**, **216** and **222** showed moderate antioxidant activity and the rest of the compounds exhibited weak antioxidant activity (Fig. 28) [118]. In the bleomycin-dependent DNA damage assay compounds **210a,b**, **214**, **215**, **217**, **218**, **219a**, **220** have shown high ability to protect DNA from damage induced by bleomycin. Some important SAR were postulated: (i) compounds **210** were more potent than AA **5** probably due to the presence of the NH and pyrazolopyridine moieties; (ii) compounds **219a,b**, **220** and **210b** have a potency equivalent or superior to that of AA **5** probably due to the presence of the pyrazolopyridopyrimidine moiety, and (iii) the good antioxidant activity of

compound **217** may be due to the presence of coumarin and pyrazolopyridopyrimidine moieties.

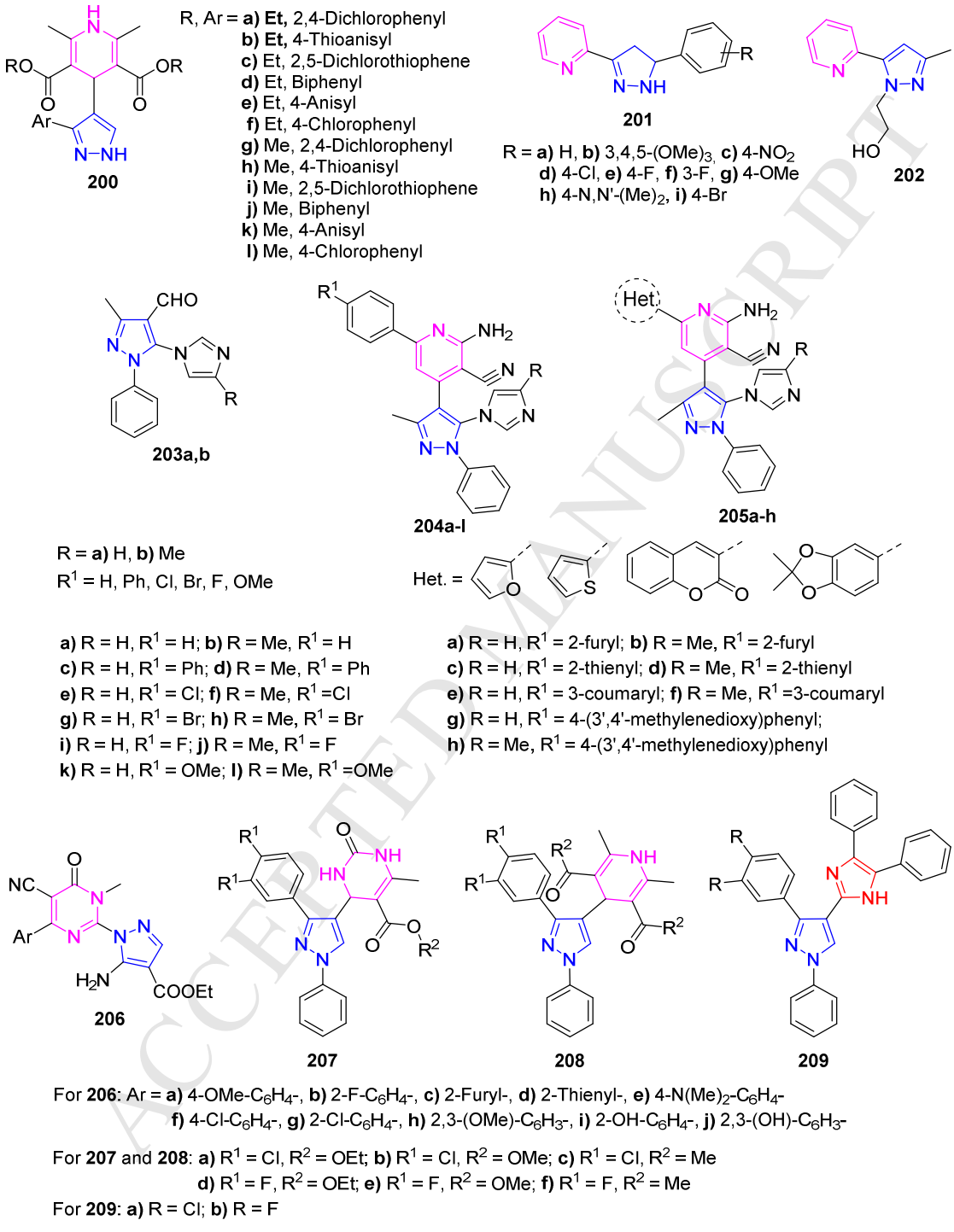


Fig. 27. Pyrazole derivatives incorporating pyridine, dihydropyridine and dihydropyrimidine moieties **200-209** [112,113,115,116,117].

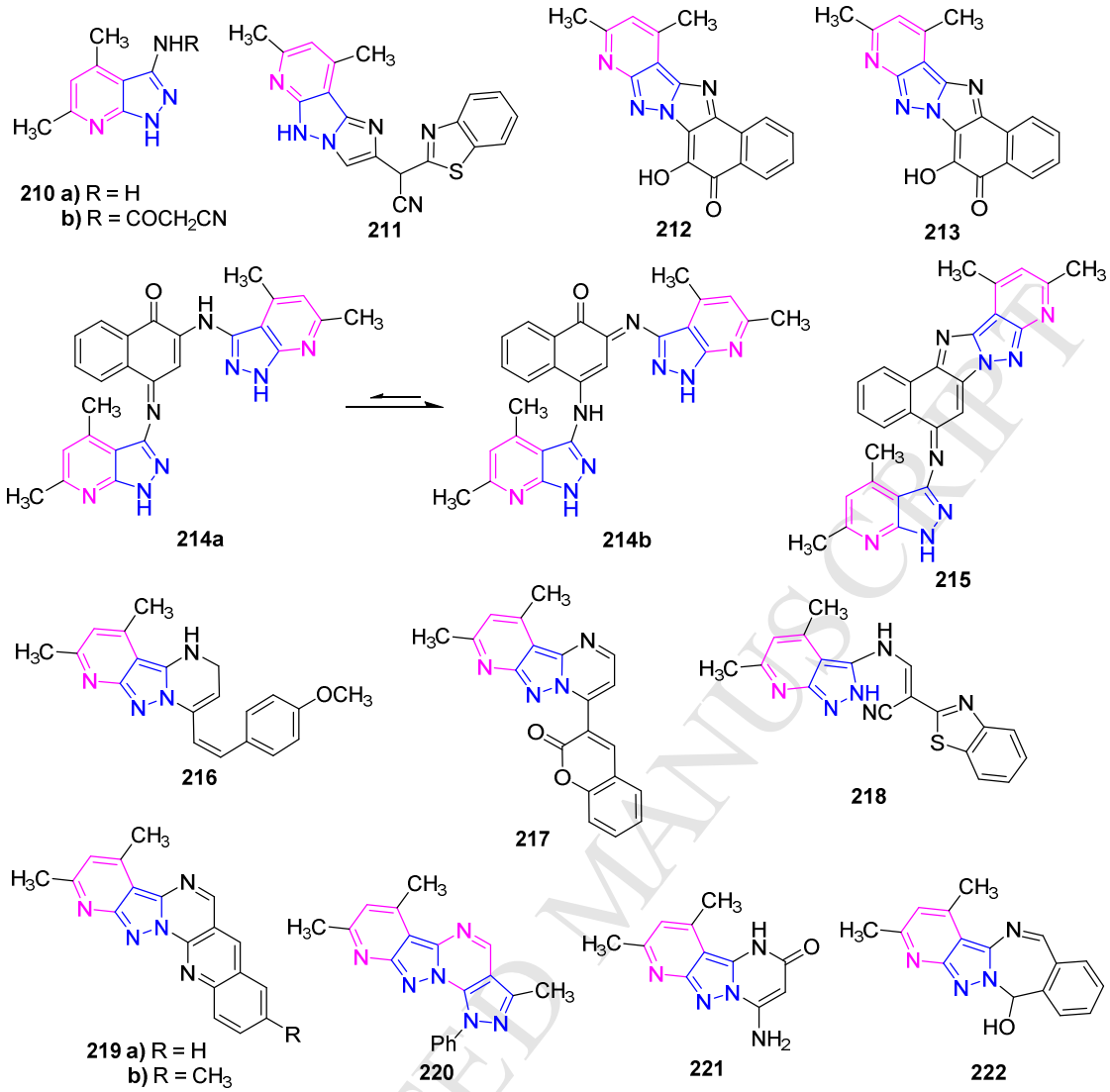


Fig. 28. Diversely substituted pyrazolopyridines **210**-**222** [118].

Compared with standards AA **5** and rutin **21**, pyrazolopyridine **223a** exhibited excellent RSA, in DPPH method, higher than AA **5**, in the following order: rutin > **223a** >AA. Standard IC_{50} values were 27.5 µM, 42.2 µM, 54.1 µM, respectively, whereas standard IC_{50} value for **223b** is 129.6 µM (Fig. 29) [119]. The DPPH inhibition is dose dependent and both compounds **223a**,**b** are safe and did not show any cytotoxic effects against normal cells, so the dose could be increased to possible enhancement of RSA without danger of cytotoxicity.

The presence of pyrazolopyrimidine moieties at C-5 of the 1,3,4-oxadiazole ring, as presented in compound **225**, was found to enhance the antioxidant activity, while the introduction of pyrano[2,3-*c*]pyrazole derivatives at the same position diminished the antioxidant activity as in compound **224** (Fig. 29) [120]. Compound **225** has shown an excellent antioxidant activity in ABTS method and ability to protect DNA from the

induced damage by Bleomycin. This high activity may be due to the hydroxy group attached to an aromatic ring that can act as scavenging of free radicals [120].

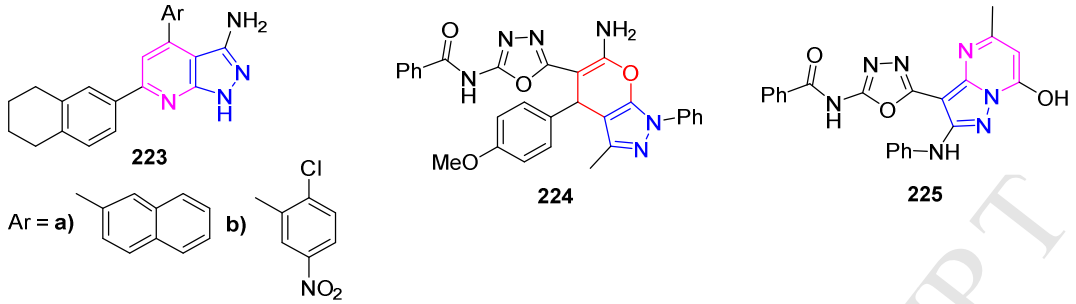


Fig. 29. Tetraline-pyrazolopyridine conjugates **223** and 2-benzoylamino-5-hetaryl-1,3,4-oxadiazoles **224-225** [119,120].

Hybrids incorporating the pyrazolo[3,4-*d*]pyrimidin-4-one moiety **226-238** joined with the thiazole **231**, tetrazole **230**, thiophene **232**, **235**, chromone **233**, pyridine or pyrazole **228**, **236** ring systems through different linkages (Fig. 30) presented various degrees of activity, in ABTS assay, comparing with AA **5** [121]. In general, most of the compounds having the thiophene, tetrazole and pyrazole moiety exhibited higher antioxidant potentials than those containing thiazole, pyridine and chromene moieties. The two most active compounds, the pyrazole **228** (92.30 % inhibition) and thiophene **238** (92.00 % inhibition) derivatives showed antioxidant activity nearly equal to that of AA **5** (92.70% inhibition).

Inhibition of phosphodiesterase-9 in neutrophils from Sickle cell anaemia (SCA) patients with compound **239** (BAY 73-6691) (Fig. 30) was able to increase the NO bioavailability and attenuate oxidative stress and inflammation in neutrophils from patients not treated with hydroxyurea [122].

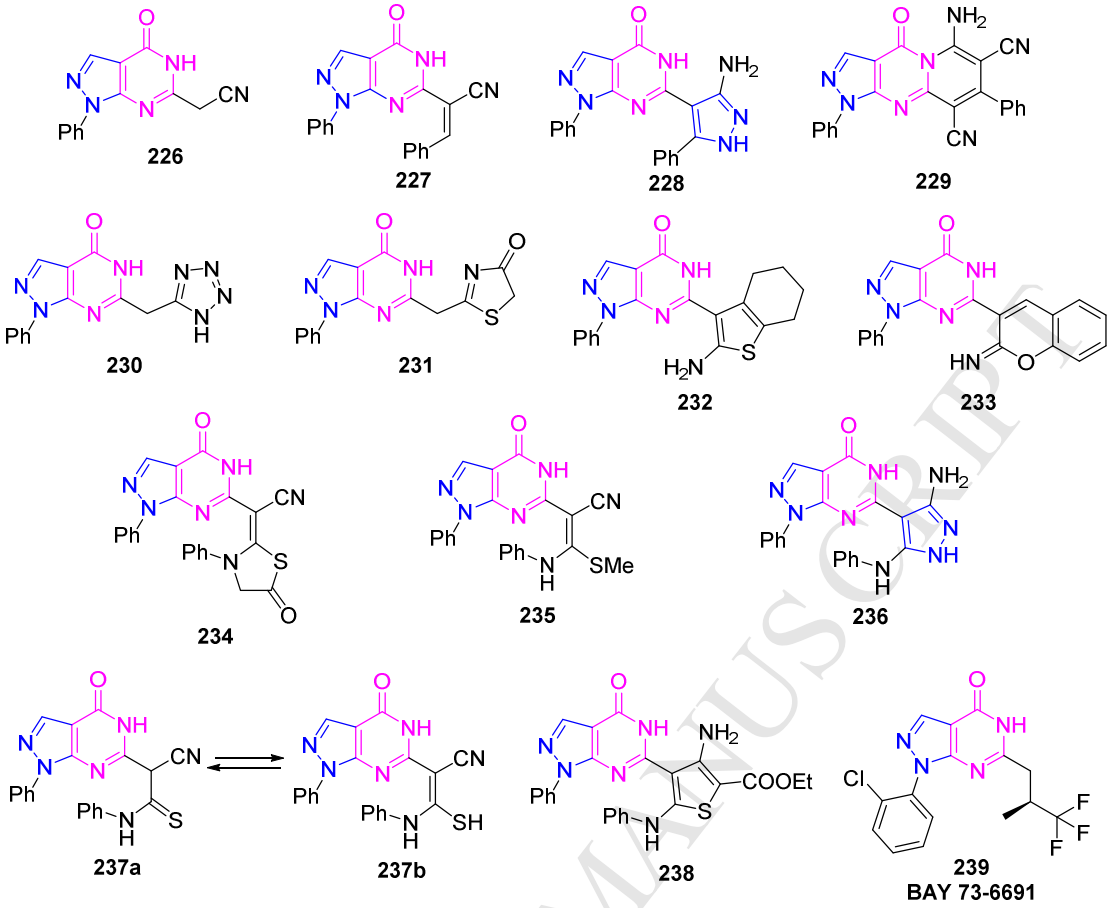


Fig. 30. Diversely substituted heterocycles incorporating the pyrazolo[3,4-*d*]pyrimidin-4-one moiety **226-238** and 1,5-dihydro-4*H*-pyrazolo[3,4-*d*]pyrimidin-4-one (BAY 73-6691) **239** [121,122].

2.1.24. (Pyrazolyl)methyl-9H-purines conjugated derivatives

9-Substituted(pyrazol-5-yl)methyl- and (2-pyrazolin-5-yl)methyl-9*H*-purines (Fig. 31) were tested *in vitro* for their ability to scavenge DPPH radical and to inhibit lipid peroxidation [123]. Mild reducing activities (13-24%) were found for compounds **240a,b**, **243a-d**,**f** after 20 min., while compounds **243e**,**g**, **244c** present 43-44% and compounds **241**, **242**, **244a**,**b** 62-79%. The presence of the pyrazole ring increases the antioxidant activity compared to the corresponding pyrazoline analogue (**241** = 60% while **240b** = 20%). Similarly, pyrazoles **244a,b** were more potent than pyrazolines **243a,b** being also the most potent antioxidants among the tested compounds. Regarding inhibition of lipid peroxidation, all compounds showed significant activity when compared to trolox **10** (64%). Comparing the activity of **243b** (piperidinyl, 72 ± 2.0%) and **243c** (pyrrolidinyl, 73 ± 1.4%) it was found that the magnitude of the ring (5- or 6-membered) does not significantly influence the activity. However, **243d** was less active (54 ± 1.0%) probably due to the presence of a bulky Boc group, whereas **243a**

(morpholinyl, 100 ± 1.5%) highly inhibits lipid peroxidation. Pyrazoline **240a** (94 ± 2.1%) seems to be more potent inhibitor of lipid peroxidation than **240b** (58 ± 1.7%). The presence of Ar = 4-Me–C_6H_4– group decreases the activity. Minor changes were observed within **240a** and **243a** with the replacement of the 6-Cl group by the morpholinyl moiety. On the contrary, significant high differences were observed between the antioxidant and inhibitory values of **240b**–**243e** (5.8 ± 0.1%). It is important to note that small changes in Ar substituent leads to significant decrease in inhibition of lipid peroxidation (e.g. **243a–e**, **243b–f**, **243c–g**). Comparing pyrazolines **243e-g** to pyrazoles **244a-c**, big differences are observed within the % inhibition values of **243e** (5.8 ± 0.1%) and **244a** (99 ± 2.2%), **243g** (49 ± 1.8%) and **244c** (87 ± 1.5%).

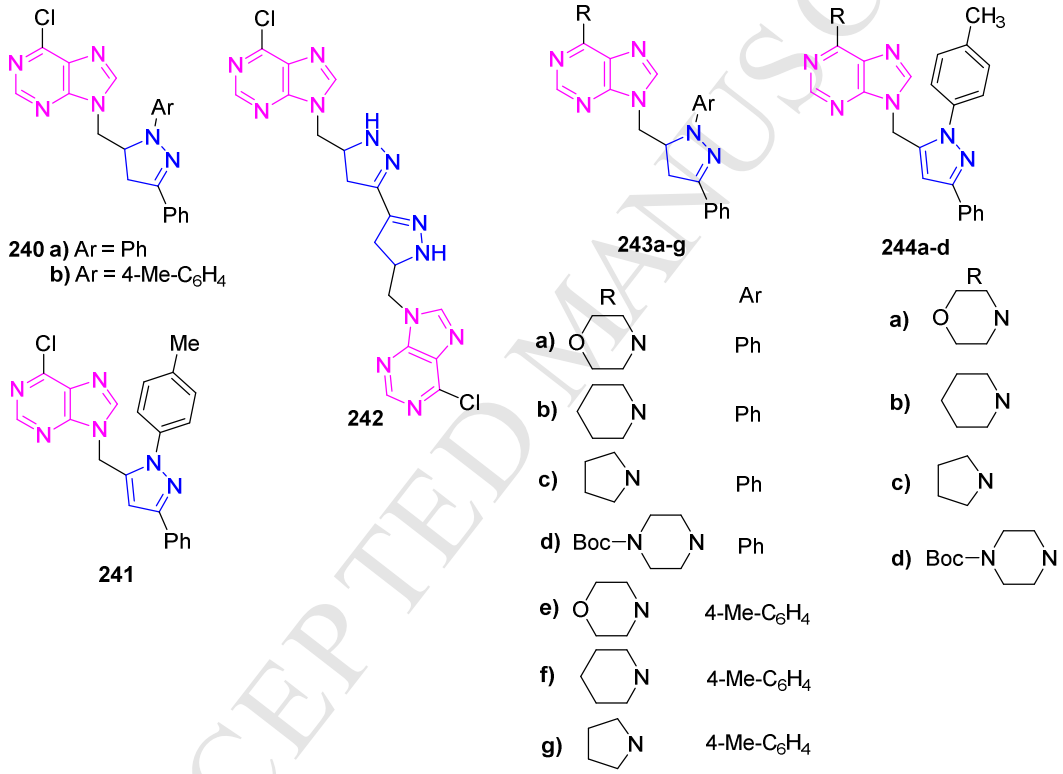


Fig. 31. 9-Substituted (pyrazol-5-yl)methyl- and (2-pyrazolin-5-yl)methyl-9*H*-purines **240-244** [123].

2.1.25. Pyrazolo[1,5-c]quinazolines

Compounds **245a,b**, **246b,d-m** and the uncyclized compounds **247** (Fig. 32) were evaluated for their ability as xanthine oxidase (XO) inhibitors. Compounds, **246b**,**e-h** and **247a** showed significant XO inhibition, but **246g**,**h** were found to be the best XO inhibitors with IC_{50} 10.96 μM and 20.89 μM, respectively, in comparison to allopurinol (IC_{50} = 31.62 μM), standard inhibitor of XO. Compounds **246g**,**h**, also demonstrated

very good antioxidant activity (**246g**, 99% and **246h**, 96% at 4 mM concentration) as they showed significant decrease in the level of DPPH$^{\bullet}$ radical as compared to BHT **7** (95% at 5 mM concentration). In silico studies highlighted the role of amino acid residues involved in interactions with **246g** and the results are in compliance with the previous reported studies [124].

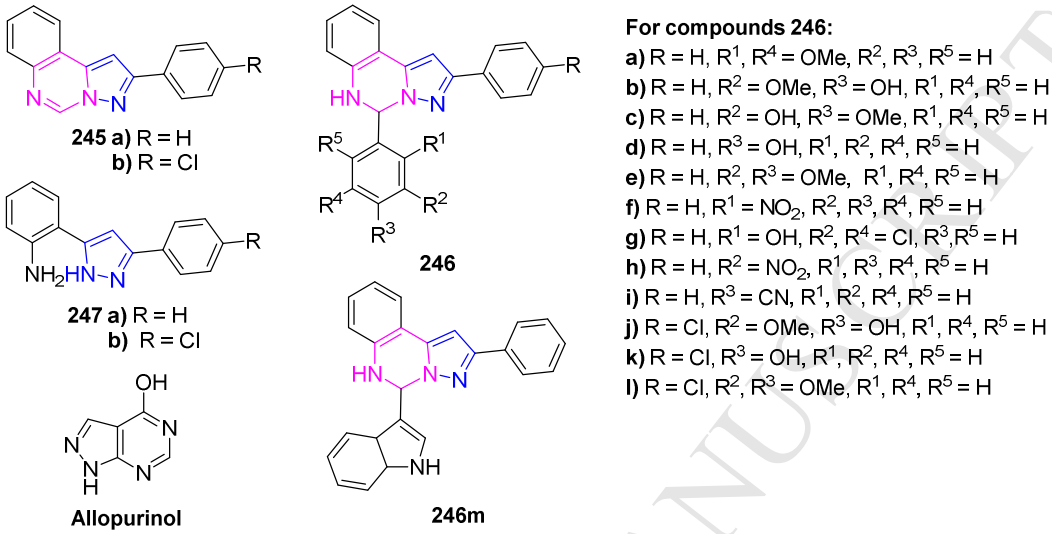


Fig. 32. 5,6-Dihydropyrazolo/pyrazolo[1,5-*c*]quinazoline derivatives **245-247** [124].

2.1.26. Pyrazoles incorporating the phenothiazine moiety

Pyrazoles anchored to phenothiazine moieties through different linkages **248-250** (Fig. 33) displayed good antioxidant activity, using ABTS method, when compared to AA **5** [125]. Compounds **248** and **256** also exhibited high protection against DNA damage induced by the bleomycin iron complex. Some SAR studies pointed out that: (i) compound **252** showed higher antioxidant activity than **249** due to the presence of bispyrazole moieties; and (ii) pyrazoles endowed antioxidant activity to these compounds since pyrazole derivatives have shown better activity than their precursors, the α,β-unsaturated ketones.

2.1.27. Pyrazoles fused with 1,4-thiazepines

1,4-Thiazepan-3-ones **261a-g** (Fig. 34), showed strong capacities for scavenging DPPH$^{\bullet}$, O_2•$^{-}$ and HO• compared with AA **5** [126]. Compounds **261d** and **261g** were the most active for scavenging all the three radicals and are also much more active than AA **5**. While it is difficult to find a rational relationship between the structure and the activity of these compounds, it is obvious that these compounds present a remarkable antioxidant activity.

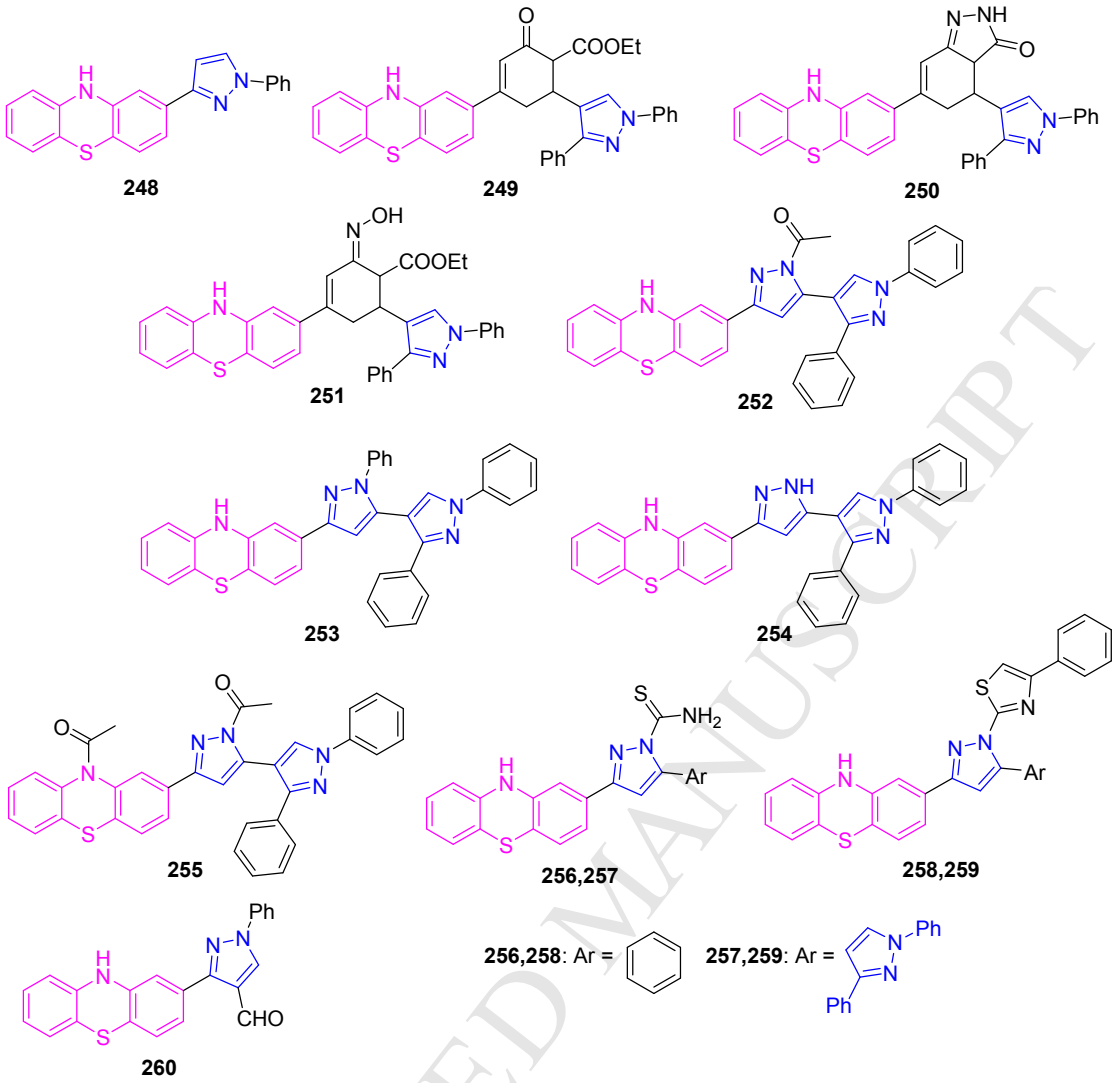


Fig. 33. Pyrazoles anchored to phenothiazine moieties **248-260** [125].

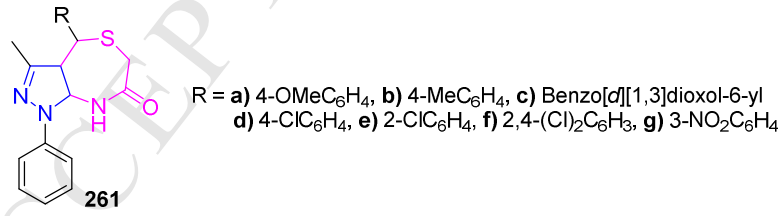


Fig. 34. 1,4-Thiazepan-3-ones fused with pyrazole scaffold **261** [126].

2.1.28. Pyrazolones and pyrazole-pyrazolone conjugates

Theoretical investigations of the structural and antioxidant properties of three synthetic pyrazolones showed that one derivative presented antioxidant activity [127]. Also pyrazole-pyrazolone conjugates **262a-g** (Fig. 35) exhibited acceptable antioxidant activity in DPPH, reducing power and DNA protection assays [128]. In DPPH assay, all derivatives showed FRSA but when compared with BHT **7** they were 50% lesser active.

At a concentration range of 30-50 µg/mL, **262f** showed higher reducing power and **262a** showed lower reducing power. Moreover DNA protective ability of **262f** (45-50%) was slightly better than that of **262a** (40-45%).

Out of a series of antipyrine **(263)-**based derivatives **264**-**267** (Fig. 35), compound **264** was the most active in ABTS assay (80.93 % inhibition) in comparison with AA **5** (92.30%), while compounds **265** and **266** showed moderate activities (40.04% and 52.54%, respectively) [129]. The introduction of aminopyrazole moiety enhanced the antioxidant properties of aminoantipyrine ring system. The presence of the cyclohexanone, as in the pyrazolotriazine **266**, decreased the antioxidant activity being this compound less active than pyrazolotriazine **265**. Moreover, compounds **264**-**267** exhibited high protection against DNA damage in the bleomycin-dependent DNA damage assay.

The *in vitro* antioxidant potential of new thiazolidin-4-ones **268a-l** based on the 4-aminophenazone (4-amino-2,3-dimethyl-1-phenyl-3-pyrazolin-5-one) scaffold (Fig. 35) was evaluated by FRAP, phosphomolybdenum reducing antioxidant power (PRAP), DPPH and ABTS methods [130]. Modification of the pyrazolin-5-one moiety through introduction of thiazolidin-4-one rings via a propionamide chain has shown a great influence on antioxidant activity since all compounds were more active than phenazone, which was used as reference. In general, the activity is concentration-dependent and it also depends on the substituents on the thiazolidin-4-one phenyl ring. In all the assays with exception of DPPH assay, compound **268e**, which has a 2-OMePh substituent, was the most active, being about 8 to 14 times more active than the unsubstituted compound **268a**. In the DPPH assay, compound **268k** (3-OMe, 4-OH) was found to be the most active being 8 times more active than the unsubstituted compound **268a**. In PRAP assay, all compounds were more active than α-tocopherol **6** (0.0304 ± 0.0024), however in the other assays they were less active than α-tocopherol **6**, at the same concentrations [130].

Compounds **269a-c** (Fig. 35) exhibited good reducing power although lower than AA **5**, BHT **7** and TBHQ **17**. The presence of enamine and α,β-unsaturated ketone functions in the pyrazoline moiety, in addition to the alkyl group, enhance the electron-donor ability of these compounds and their reducing power capacity. Compound **269a** was more active than **269b**,**c** due to the 5-chloro-substitution at the indole, which may contribute for stabilization of the free radical form after donating the electron [131].

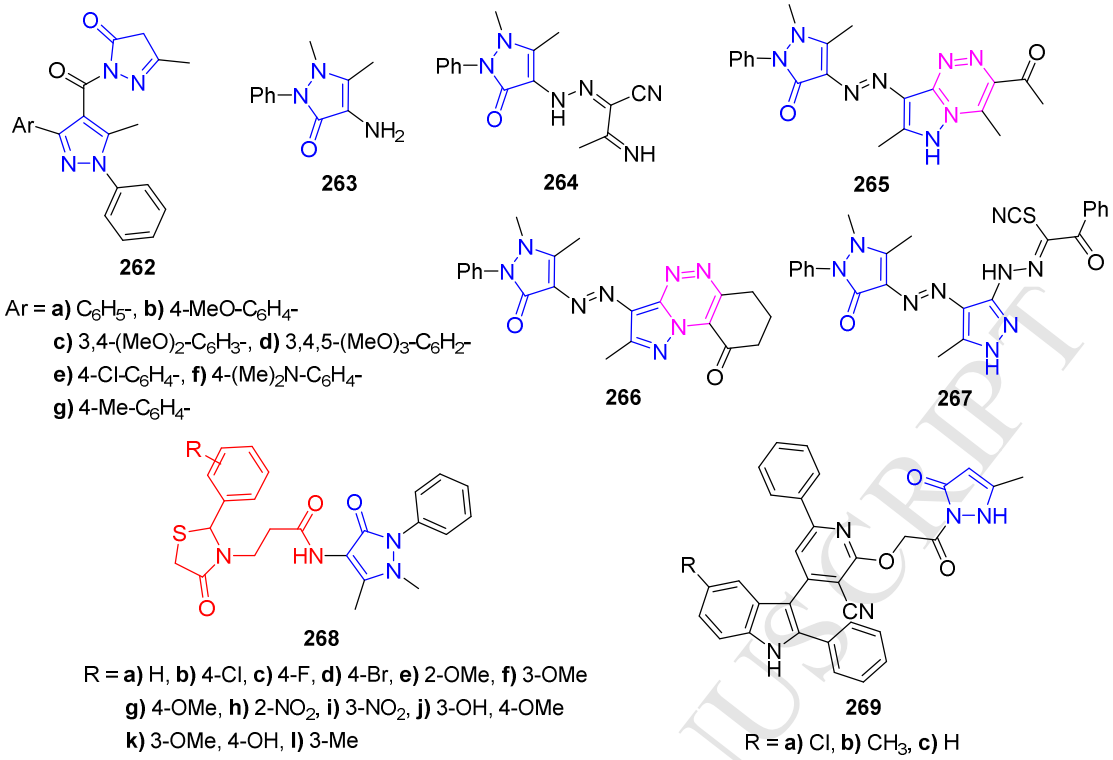


Fig. 35. Pyrazolones and pyrazole-pyrazolone conjugates **262-269** [128,129,130,131].

2.1.29. Pyrazolidines

Two pyrazolidines, **270** and **271** (Fig. 36) act as antioxidants by quenching the lipid peroxyl radical. The IC_{50} of **271** was of the same order of magnitude as that of probucol **22** while the IC_{50} of **270** was similar to that of α-tocopherol **6**. However, at 10^{24}–10^{25} M **270** completely inhibited peroxidation being more effective than α-tocopherol **6**. These compounds also inhibited lipid peroxidation of rat brain homogenates [132].

Morpholine-connected pyrazolidines **272c** and **273a** (Fig. 36) showed very good $ABTS^{+\bullet}$ RSA of 81.6 and 91.3%, respectively, as compared to trolox **10** (85.2%) [133]. A mechanism to explain the antioxidant activity of **273a** and analogues is presented in Fig. 37. Compounds **272c** and **273a** also presented good inhibition of linoleic acid peroxidation, 75.4 and 84.5%, respectively, better that trolox **10** (62.3%) at a concentration of 100 μg/mL [133].

2.1.30. Miscellaneous

The modification of minocycline **274a** and tetracyclines **274b,c** into their hydroxypyrazolino-derivatives (Fig. 38) significantly improved their antioxidant activities. Compound **275** showed improved antioxidant activity compared to the parent tetracyclines **274,** in DPPH and ABTS assays, but not in superoxide assay [134]. On the

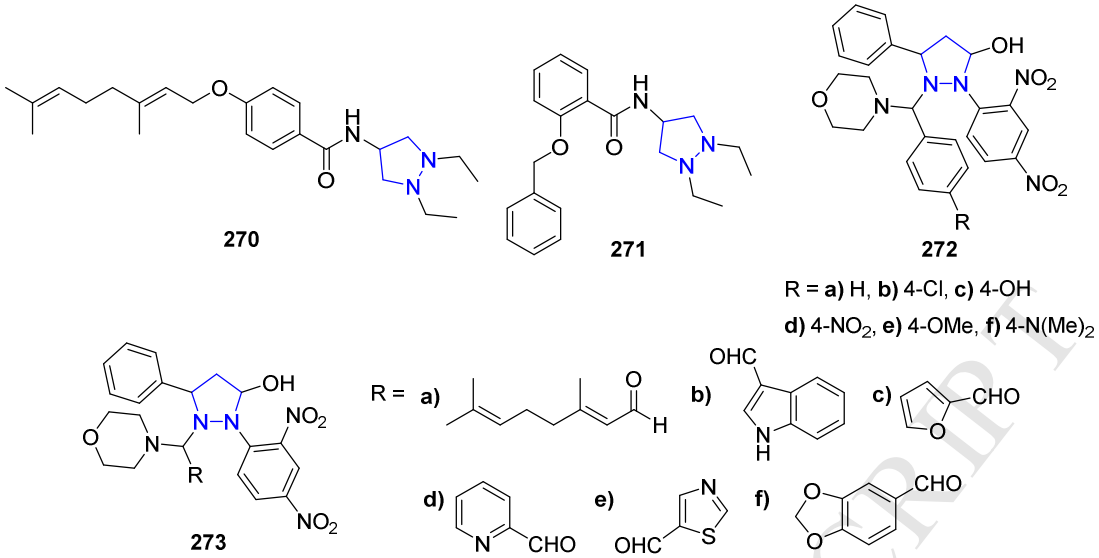


Fig. 36. Pyrazolidines and morpholine-connected pyrazolidine derivatives **270-273** [132,133].

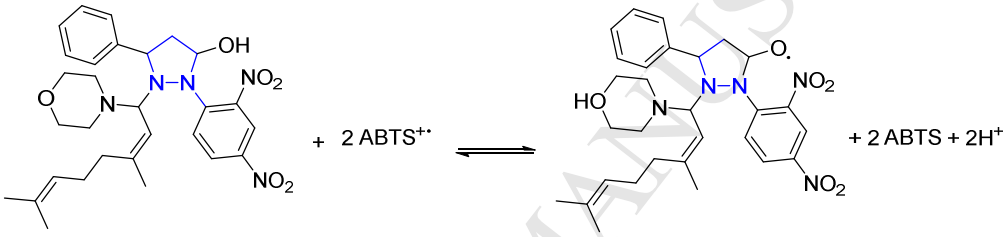
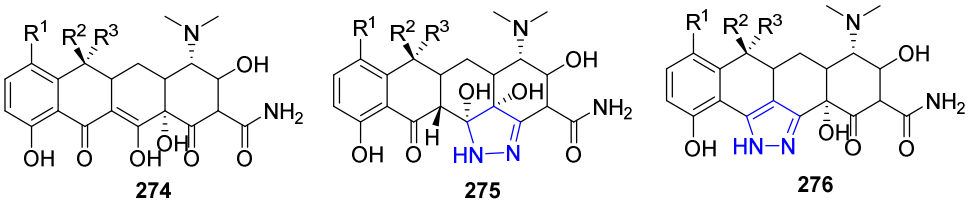


Fig. 37. Proposed mechanism for the antioxidant activity of compound **273a** and analogues [133].

contrary, the presence of the pyrazole ring in **276b** significantly improves the antioxidant activity of the parent tetracycline **274b** in superoxide assay, but not in DPPH or ABTS assays. The antioxidant activity of compounds **275** and **276** was attributed to the presence of the extra heterocyclic ring and the supplementary NH and OH functions enhancing their ability to act as electron donators. Moreover, hydroxypyrazolino tetracyclines **275** are able to chelate Cu^{2+}, a known catalyst of free radical formation, thus contributing to the oxidative stress drive. 12*S*-Hydroxy-1,12-pyrazolinominocycline **275a** is a promising tetracycline-based antioxidant devoid of antibiotic properties and metalloproteinases inhibitory activity, which could be beneficial in the treatment of complications related to oxidative stress.



a) $R^1 = N(Me)_2$, $R^2 = H$, $R^3 = H$; **b)** $R^1 = H$, $R^2 = OH$, $R^3 = Me$; **c)** $R^1 = Cl$, $R^2 = OH$, $R^3 = Me$

Fig. 38. Hydroxypyrazolino **275** and pyrazole derivatives **276** of minocycline **274a** and tetracycline **274b,c** [134].

From pyrazole-chalcones **277a-j** (Fig. 39), those bearing phenyl **277a**, 4-methoxyphenyl **277c** and 3-chlorophenyl **277g** groups showed 25-35% DPPH activity [135]. The antioxidant activity of these compounds is related with their electron or hydrogen radical releasing ability to DPPH$^{\bullet}$ so that they become stable diamagnetic molecules. The compounds possessing higher E_{HOMO} and E_{LUMO} were found to be more effective in the stabilization of DPPH$^{\bullet}$ radicals because the electron donating ability has been strongly attributed to E_{HOMO} (electron donation capability) and E_{LUMO} (electron accepting capability).

In DPPH assay all the pyrazole derivatives incorporating one, two and three pyrazole rings **278-282** (Fig. 39) were more potent than AA **5**. Furthermore, these compounds inhibit peroxinitrite-induced tyrosine nitration and were more potent than trolox **10** [136].

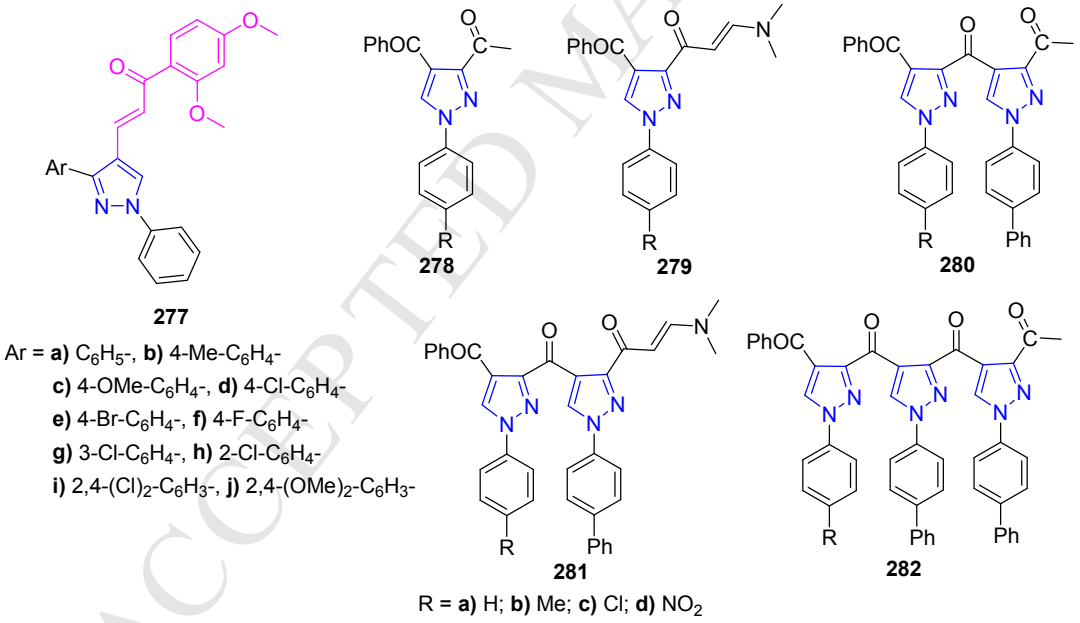


Fig. 39. Pyrazole-chalcone conjugates and pyrazoles incorporating pyrazolylpyrazole moiety **277-282** [135,136].

3,5-Bis(substituted)pyrazoles **283** (Fig. 40) showed varying degree of RSA in DPPH assay when compared with AA **5**. The maximum activity was observed for compound **283b**. The presence of either EDGs or EWGs on the phenyl ring mostly favour the activity particularly with a strong EDG [$-N(Me)_2$] or EWG (NO_2). Antioxidant activity of compounds **283** is related with their electron or hydrogen radical donating ability to

DPPH$^{\bullet}$ radical, so that they become stable diamagnetic molecules. These compounds also showed moderate ferric chloride-induced lipid peroxidation inhibition at 40 µg/mL, at varying degree when compared with α-tocopherol **6**, and in the order **283b** > **283f** > **283d**. The presence of an EDG on the phenyl ring at C-4 such as –N(Me)$_2$, –OH and –OMe at C-3,4,5 enhanced the activity when compared to compound **283e**. The presence of a strong EWG (4-NO$_2$) on the phenyl ring did not favour the activity. This might be the reason for the inactivity of compound **283i** [137].

The 1-alkylamino-4-chloro-benzo[*g*]phthalazine functionalized with pyrazole ring at the end of the side chain **284** (Fig. 40) demonstrated *in vitro* anti-leishmanicidal activity in both L. infantum and L. braziliensis species. The activity of **284** was due to its remarkable inhibitory effect on the antioxidant enzyme Fe-SOD of promastigote forms of the parasites, due to the presence of the pyrazole ring endowed with electron-donating sp2 nitrogen, which suggests excellent complexing properties against the transition metal [138].

1,3,5-Triaryl-4,6-dioxopyrrolo[3,4-*d*]-7,8-dihydropyrazoles **285a-f** (Fig. 40) showed promising RSA at 30-50 µg/mL; compounds **285a-d** were more active with a RSA up to 55% whereas **285e,f** presented a RSA up to 40% with reference to BHT **7** [139].

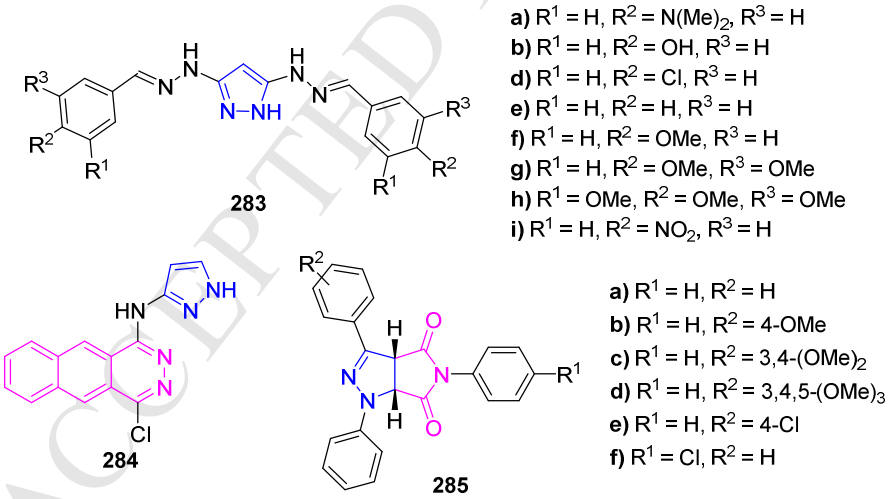
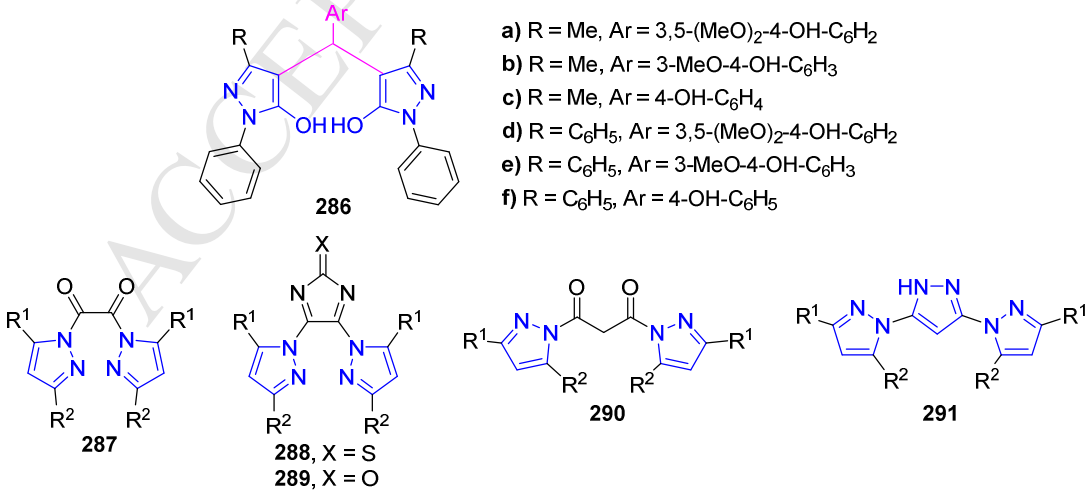


Fig. 40. 3,5-Bis(substituted)pyrazoles **283,** phthalazine functionalized with pyrazole ring **284** and 1,3,5-triaryl-4,6-dioxopyrrolo[3,4-*d*]-7,8-dihydropyrazoles **285** [137,138,139].

4,4'-Arylmethylene-bis(1*H*-pyrazol-5-ols) **286b-f** (Fig. 41) exhibited significant DPPH and ABTS$^{+\bullet}$ RSA, comparable to that of trolox **10**, while the activity of compound **286a** was almost 2 times higher than the standard. The IC$_{50}$ values of **286a-f**, in DPPH assay, were lower than that of **10**, whereas in the ABTS assay compounds **286a**,**b**,**d**,**e**

have almost the same IC_{50} as **10**. The best antioxidants were **286a**,**d** that contain two methoxy groups in the aromatic phenyl ring. The substituent at C-4 of pyrazoles also produces effects on their activity since methyl substituted pyrazole **286a** showed much better antioxidant activity than the phenyl substituted derivative **286d** [140].

Among compounds **287-291** (Fig. 41) higher DPPH RSA at 10 µg/mL concentration was observed for compounds **287h, 288h, 289h, 290h, 291h**, having β-dicarbonyl and EDGs at *para*-position of phenyl moiety, when compared to AA **5**. The presence of phenyl rings is beneficial for this type of activity, as well as the presence of EDGs or EWGs at *para*-position of the phenyl rings. The antioxidant activity of these compounds is related with their electron or hydrogen radical donating ability to DPPH$^{\bullet}$ radical, so that they become stable diamagnetic molecules. This might be the reason for the higher antioxidant activity of compounds **290a-j** [141]. On the other hand, compounds **290h**,**g** and **287h** showed maximum anti-lipoperoxidation comparable to that of α-tocopherol **6** at 40 µg/mL concentration. The presence of strong EWGs at *para*-position on the phenyl rings is not beneficial since compound **287j**, which has fluorine at that position, exhibited the lowest inhibition. Thus, the presence of EDGs at the *para*-position of the phenyl rings and the presence of carbonyl groups at β-positions or acidic protons at α-position seem to enhance the anti-lipoperoxidation activity. This activity was found to be lower in case of compounds which do not have phenyl rings or which do not have a substituent on the phenyl rings. This might be the reason for the inactivity of compounds **287a**, **288j**, **289j**, **290j** and **291j**.



a) $R^1 = R^2$ = Me; **b)** R^1 = Ph, R^2 = Me; **c)** $R^1 = R^2$ = Ph; **d)** R^1 = 4-MeC_6H_4, R^2 = Me
e) R^1 = 4-MeC_6H_4, R^2 = Ph; **f)** R^1 = 4-ClC_6H_4, R^2 = Ph; **g)** R^1 = Ph, R^2 = 4-$MeOC_6H_4$
h) $R^1 = R^2$ = 4-$MeOC_6H_4$; **i)** R^1 = Ph, R^2 = 3,4,5-$(OMe)_3C_6H_2$; **j)** R^1= Ph, R^2 = 4-FC_6H_4

Fig. 41. 4,4'-Arylmethylene-bis(1*H*-pyrazol-5-ols) **286** and other diversely substituted pyrazoles and 1,3-diketones **287-291** [140,141].

Compounds **292a-i** (Fig. 42) possess moderate to low DPPH FRSA [142]. Among them, derivatives **292d**,**f** exhibited very good activity comparable to BHA **8**. The antioxidant activity of these compounds may be related to their redox properties which allow them to act as reducing agents or hydrogen atom donors, their ability to chelate metals, inhibit lipoxygenase and scavenge free radicals.

Benzophenone analogues incorporating the pyrazole scaffold **293a-j** (Fig. 42) have shown good to moderate scavenging activity against a variety of ROS and RNS such as $^{\bullet}OH$, $O_2^{\bullet-}$ and $DPPH^{\bullet}$ radicals [143]. Compounds **293d**,**f,g** showed good DPPH FRSA (40.25-48.85%) when compared to AA **5** (81.52%), **293f**,**g** showed significant ROS scavenging activity (52.24% and 51.41%, respectively), compared to AA **5** (51.95%), whereas all the other compounds are weak ROS scavengers. Compounds **293b**,**d**,**i**,**g** that contain halogen substituents in the phenyl ring showed 36–47% inhibition of hydroxyl radical as compared to AA **5** (78.34%). It is difficult to rationalize the FRSA of these compounds with the electronic nature of the substituents in the phenyl ring; the wide variation in the activity may be due to the variation in the proton–electron transfer by the derivatives due to difference in their structures and stability.

Among pyrazolines **294a-l** and isoxazolines containing a pyrazole ring **295a-l** (Fig. 42), derivatives **294c**,**d**,**e**,**f**,**h**,**k**, and **295c**,**e**,**h**,**k** were considered good antioxidants, **294g** was considered a poor antioxidant while the remaining compounds showed moderate activity, in FRAP assay, using AA **5** as reference [144]. The substitution pattern of the aryl ring at the third position in the pyrazoline/isoxazoline ring, namely the electronic nature of the substituents, was found to affect antioxidant activity. The introduction of a fluorine atom in that ring (**294e**,**k**, **295e**,**k**) increased the antioxidant activity, as well as the hydroxy group (**294f**), the only EDG that contributes to augment this activity. The replacement of the nitrogen atom in the pyrazoline by the oxygen atom to form the isoxazoline led to a decrease of the antioxidant activity, since compound **294d** showed higher activity than **295d** [144].

The antioxidant activity of compounds **296**, **297** and **298** (Fig. 42) was tested by DPPH method and compounds **297** and **298** exhibited significant antioxidant activity at 100 μM concentration when compared with AA **5** [145].

The antioxidative system of coffee leaves sprayed with the pyrazole fungicide, pyraclostrobin **299** (Fig. 42), was highly improved owing to the reduction of the activity of the peroxidase and catalase-type enzymes minimizing coffee leaves rust [146].

Hispolon **300** and its isoxazole **301** and pyrazole **302** derivatives (Fig. 42) showed high reactivity towards a variety of free radicals, making them potential antioxidants. Experimentally observed kinetic parameters and calculated molecular descriptors proposed that **301** and **302** are better than **300** for scavenging $N_3^{\bullet}$ and $CCl_3O_2^{\bullet}$ radicals. Lower AIP and higher HOMO value are the deciding factor for such higher activity of **301** and **302** in comparison to **300**. However, reactivity with $DPPH^{\bullet}$, $O_2^{\bullet-}$ or lipid peroxyl radicals indicated that **300** has higher scavenging ability mainly due to the favourable pKa values. The mechanisms of antioxidant action of these three derivatives towards the different radicals were reported [147]. Along with the known molecular descriptors for effective antioxidant ability, such as higher electron density, stable radicals, bond dissociation energies, the pKa of the molecules is also an important parameter in deciding its antioxidant mechanism.

Ruxolitinib **303** (Fig. 42) combated thioacetamide (TAA)-induced hepatotoxicity effects by ameliorating hepatic injury, cellular death, oxidative stress and inflammatory cytokines [148].

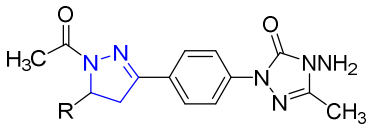
A hybrid of lipoic acid and 4-phenyl-1*H*-pyrazole **304** (Fig. 42) was identified as a novel potent bifunctional ROCK inhibitor (ROCK1 = 2.11 μM and ROCK2 = 0.437 μM) with antioxidant and neuroprotective activities [149].

Among the1,3-diarylpyrazole-4-carbaldehyde benzoyl-hydrazones **305** (Fig. 42), it was found that the substitution at 4-position with EWG ($-NO_2$) enhanced the antioxidant activity whereas the presence of EDG (Me) decreased the activity [150].

(Z)-(2-((1,3-diphenyl-1*H*-pyrazol-4-yl)methylene)hydrazinyl)(pyridin-2-ylamino) methanethiol **306** (Fig. 42) displayed scavenging activities greater than 50% of the superoxide anion radical ($^{\bullet}O_2^-$), but was lower than 50% for hydroxyl radical ($^{\bullet}OH$) [151].

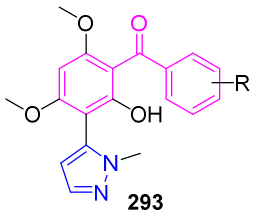
Pyrazolines **307-309** (Fig. 42) demonstrated significant antioxidant activities by DPPH and SOD scavenging assays when compared to GA **12**, AA **5** and BHA **8** [152]. In DPPH method, compound **307** had the highest activity comparable with standards. In the SOD assay, compound **307** also exhibited the highest activity. The reducing power activities of compounds **307-309** were determined by both PRAP and FRAP assays. In both assays,

compound **307** showed the highest reducing ability. The results indicated that *ortho* position of the pyridine ring in the molecules has a positive effect on the antioxidant activity [152].



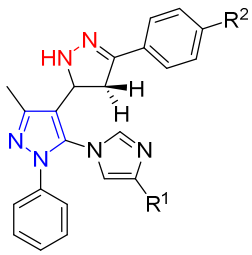
292

R = **a)** C_6H_5-, **b)** 2-Cl-C_6H_4-, **c)** 3-Cl-C_6H_4-
d) 4-Cl-C_6H_4-, **e)** 4-NO_2-C_6H_4-, **f)** 4-Me-C_6H_4-
g) 4-OH-C_6H_4-, **h)** 4-OMe-C_6H_4-, **i)** 3,4-$(OMe)_2$-C_6H_3-

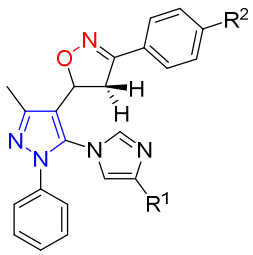


293

R = **a)** H, **b)** 2-F, **c)** 3-F, **d)** 3-Br, **e)** 3-CF_3, **f)** 4-OMe
g) 2,4-F, **h)** 2,4-Cl, **i)** 2,3-Cl, **j)** 2,5-Cl



294



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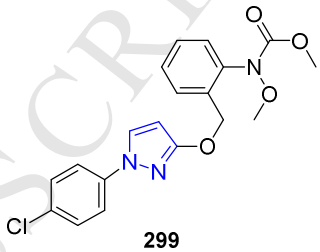
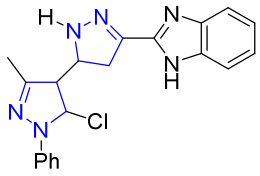


299

a) R^1 = H, R^2 = H; **b)** R^1 = H, R^2 = Ph; **c)** R^1 = H, R^2 = OMe; **d)** R^1 = H, R^2 = Br
e) R^1 = H, R^2 = F; **f)** R^1 = Me, R^2 = OH; **g)** R^1 = Me, R^2 = H; **h)** R^1 = Me, R^2 = Ph
i) R^1 = Me, R^2 = OMe; **j)** R^1 = Me, R^2 = Br; **k)** R^1 = Me, R^2 = F; **l)** R^1 = Me, R^2 = OH



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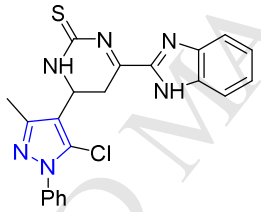

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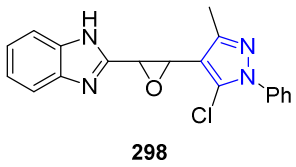
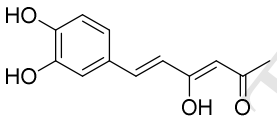
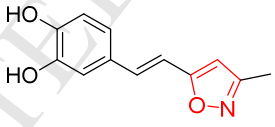


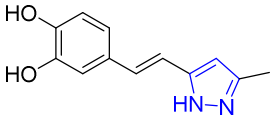
298



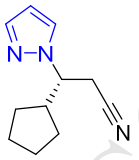
300 (enol form)



301



302



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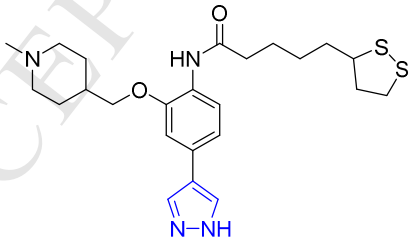
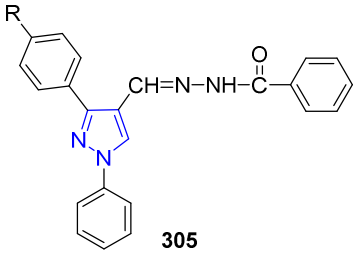
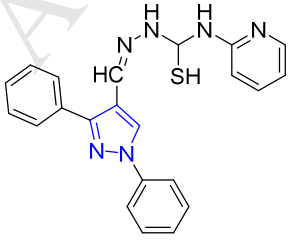


304

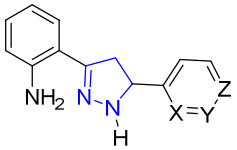


305

R = H, Cl, NO_2, Me



306



307: X = N, Y = Z = H
308: Y = N, X = Z = H
309: Z = N, X = Y = H

Fig. 42. Diversely substituted pyrazoles **292-309** [142,143,144,145,146,147,148,149, 150,151,152].

2-(3,5-Dimethylpyrazol-1-yl)ethylseleno derivatives **310-317** (Fig. 43) exhibited GPx like catalytic activity in the order **315** > **316** > **314** > **313** > **310**> **317** > **312** > **311**[153]. The GPx mimicking reactions proceed through a selenoxide intermediate. The high activity of **315** and **316** in methanol could be due to the amino group which acts as a good base catalyst for the GPx reaction. A probable interaction between N(2) of the dimethylpyrazole and selenium may possibly stabilize the intermediate, thereby inducing GPx like activity. For the monoselenides substituted with functional groups like –COOH and –NH_2, the GPx mimicking activity increases because of their inductive effect, which facilitates selenoxide formation. In addition, these functionalities enhance solubility in protic solvents [153].

Thiazoles integrated with pyrazoline scaffolds showed varied RSA depending on their substitution pattern. The most active compound was **319h** (Fig. 43)**,** bearing hydroxy substituent on phenyl ring attached to thiazole with 45.23% of RSA and IC_{50} value of 63.11 µg/mL followed by **319f**, containing amino substituent, with 42.50% of RSA and IC_{50} value of 67.93 µg/mL. All compounds were less active than AA **5** (15.48 µg/mL). Single crystal studies revealed that for compounds **318**, **319g**,**j** the isopropyl ring is positioned at near right angle with the other rings. The non-planarity of the molecules has impact on their antioxidant activity by decreasing the ability of the compounds to donate electron to the free radicals [154].

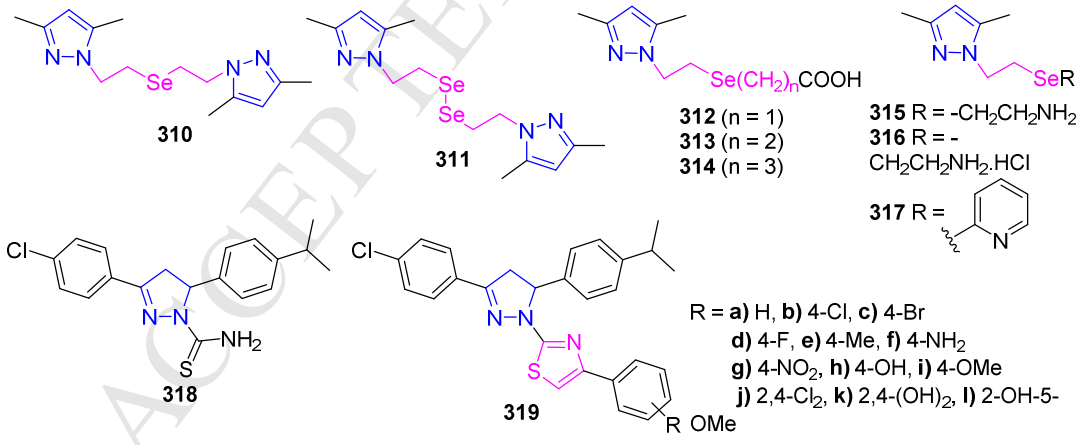


Fig. 43. 2-(3,5-Dimethylpyrazol-1-yl)ethylseleno derivatives **310-317** and pyrazolines **318**,**319** [153,154].

3. Conclusion and prospect

During recent years, a variety of chemically diverse antioxidants, containing the pyrazole pharmacophore, have been developed by various research groups. An

overview of their structures, antioxidant activity and of the structure-activity relationships is herein presented. Synthetic pyrazole-type compounds have the ability to act as antioxidant agents alone or combined with other pharmacophores in one frame. Among the other pharmacophores, there are diverse chemical entities such as, chromones, furan, thiophene, benzofuran, fused pyrano[2,3-*c*]pyrazoles, oxadiazoles, indoles, carbazoles, quinolines, quinoxalines, pyridines, pyrimidines, purines, quinazolines, phenotiazines and thiazepines. The antioxidant properties can be therefore influenced also by the occurrence of these heterocyclic rings in the molecule. For example, it was demonstrated that the introduction of oxygen-containing heterocyclic rings, like coumaryl substituent, in the pyrazole structure, can increase the antioxidant effects, since coumarins also have antioxidant activity. Among pyrazole-based antioxidants, some were obtained by structural modification of natural antioxidants, such as curcumin-templated pyrazoles. These pyrazoles were found to have higher antioxidant activity than the natural curcumin, suggesting that the insertion of the pyrazole ring is responsible for the increase of the antioxidant activity. This effect was observed also for other compounds obtained by heterocyclization of their precursors with concomitant formation of the pyrazole ring. It is difficult to establish a correlation between lipophilicity and antioxidant activity. Actually, both antioxidants of hydrophilic and lipophilic character are encountered in the literature and both act as radical scavengers in the aqueous phase or as chain-breaking antioxidants in biological membranes. Whenever possible, detailed structure-activity relationships were presented for the compounds presented in this manuscript, but in some cases it was difficult to establish structure-activity relationships, since the variation of the RSA of pyrazoles and dihydropyrazoles can be attributed to the effect of the different substitutions present in the compounds' structure. Moreover, both the oxidized (pyrazole) and the reduced (dihydropyrazole) forms possess RSA and the interchange between these forms has effects on the antioxidant activity. However, in some cases it was possible to see a trend and some more general structure-activity relationships were portrayed: (i) for 3,5-diarylpyrazoles the presence of EDGs in both aryl rings or the presence of halogens in one of the aryl rings seems to be more beneficial for the RSA than electron-withdrawing substituted or unsubstituted phenyl rings; (ii) an important role of EDGs (Me, OMe, OH) was observed for aryl/heteryl-substituted sulfonylpyrazoles due to their positive inductive and mesomeric effects; (iii) a strategy to increase the antioxidant activity of pyrazoles/dihydropyrazoles could be the hybridization with other compounds with

known antioxidant activity through the conjugation of both scaffolds; and (iv) the comparison of the activity of pyrazole with that of isoxazole, revealed that in most cases the isoxazole was more active than the pyrazole, probably due to the presence of the oxygen atom in the isoxazole ring.

In most of the studies encountered in the literature the antioxidant ability of pyrazoles is evaluated by comparison with standard antioxidant compounds; usually the AA **5** was chosen as the standard, but there are also some studies where no references were used. No references were found in the literature regarding the study of the antioxidant activity of 3(5)-(2-hydroxyphenyl)-5(3)/4-styryl-1*H*-pyrazoles. We have been working with this type of pyrazoles since many years now [155,156,157]. Recently we started a project aiming to investigate their ability as antioxidant and anti-inflammatory agents. The results obtained will be published in the near future, thus contributing to the development of this research field.

The current landscape of the development of antioxidants containing the pyrazole core is outlined in this review, with a focus on the structure-activity relationships to pursue better activity and more favourable pharmacokinetic properties. Various novel chemical entities discussed herein may provide an opportunity to scientists and researchers of medicinal chemistry field to design and developed better pyrazole-based compounds as antioxidant agents in future.

Acknowledgements

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Highlights

- Pyrazole is an important pharmacophore in the development of antioxidants.
- Pyrazoles alone or combined with other pharmacophores showed high antioxidant activity.
- Hybridization with known antioxidants can be a strategy to increase pyrazoles activity.
- Important structure-activity relationships were disclosed and presented herein.