Biometals (2012) 25:9–21
DOI 10.1007/s10534-011-9496-4

# Perspective: the potential of pyrazole-based compounds in medicine

**Frankline K. Keter · James Darkwa**

Received: 22 June 2011 / Accepted: 14 September 2011 / Published online: 15 October 2011


**Abstract** Pyrazoles are widely used as core motifs for a large number of compounds for various applications such as catalysis, agro-chemicals, building blocks of other compounds and in medicine. The attractiveness of pyrazole and its derivatives is their versatility that allows for synthesis of a series of analogues with different moieties in them, thus affecting the electronics and by extension the properties of the resultant compounds. In medicine pyrazole is found as a pharmacophore in some of the active biological molecules. While pyrazole derivatives have been extensively studied for many applications including anticancer, antimicrobial, anti-inflammatory, antiglycemic, anti-allergy and antiviral, much less has been reported on their metal counterparts in spite of the fact that metals have been shown to impart activity to ligands. Thus this perspective is intended to demonstrate the potential of pyrazole and pyrazolyl metal complexes in the areas of drug discovery and development. Several examples, that include palladium, platinum, copper, gold, zinc, cobalt, nickel, iron, copper, silver and gallium complexes, are used to bolster the above point. For the purposes of this review three areas are discussed, that is pyrazole metal complexes as: (i) anticancer, (ii) antibacterial/parasitic and (iii) antiviral agents.

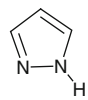
**Keywords** Pyrazole · Metal complexes · Anticancer · Antibacterial · Antiparasitic · Antiviral

F. K. Keter (✉)
Advanced Materials Division, Mintek, Private Bag X3015, Randburg 2125, South Africa
e-mail: FranklineK@mintek.co.za

J. Darkwa
Department of Chemistry, University of Johannesburg, Auckland Park Kingsway Campus, Auckland Park 2006, South Africa

## Introduction

Over the years increasing attention has been paid to pyrazoles in drug and related research since the initial reports on their properties as inhibitors of alcohol dehydrogenase (Pereira et al. 1992), potential anti-allergic agents (Vitolo et al. 1978; Di Parsia et al. 1981), analgesic agents (Takabatake et al. 1970) and even as anti-inflammatory agents (Hirschmann et al. 1964) appeared in the literature nearly 40 years ago. Subsequently a number of seminal papers have given leads to different areas of potential applications of pyrazole and pyrazole complexes in medicine. These lead papers are briefly highlighted below to indicate the extent of potential areas of applications.




**1**

There has been ample evidence that pyrazoles possess therapeutic properties for quite some time. The first

documented evidence dates back to the 1960 s where pyrazoles were shown to inhibit the action of horse liver alcohol dehydrogenase (LADH) (Theorell and Yonetani 1963; Theorell et al. 1969; Li and Theorell 1969). In addition, research published by Blomstrand (1972) and Blomstrand et al. (1979) suggested that methylpyrazole could be used to treat methanol poisoning. This is after it was demonstrated that methylpyrazole inhibits alcohol dehydrogenase (Theorell and Yonetani 1963) even though its parent compound, pyrazole (**1**), was found to be toxic. In related experiments, Eklund et al. (1976, 1982) and Dahlbom et al. (1974) demonstrated that pyrazoles and their derivatives are good ADH inhibitors. For instance, 4-ethylpyrazole, a less toxic derivative of pyrazole, is even a stronger inhibitor of LADH, with $K_I$ of 0.007 μM. It is even more interesting that it was suggested to offer a solution to alcoholism.

Since the discovery that 3-methylpyrazole and 4-ethylpyrazole have potential medicinal value, there has been a rapid growth in synthesizing new derivatives of pyrazole as anticancer (Manfredini et al. 1992; Komeda et al. 2000; Gamage et al. 2002; Moukha-Chafiq et al. 2002; Rostom et al. 2003; Duivenvoorden et al. 2005; Park et al. 2005; Keter et al. 2009a), antibacterial (Jungheim 1989; Aiello et al. 2000; Genin et al. 2000a; Kucukguzel et al. 2000; El-Gaby et al. 2000; Farghaly et al. 2001; Moukha-Chafiq et al. 2002; Haque et al. 2002; Kaymakcıoglu and Rollas 2002; Panda et al. 2002; Adnan and Abdel-Aziem 2004; Tanitame et al. 2004; Akbas and Berber 2005; Bekhit et al. 2005; Bildirici et al. 2007; Abunada et al. 2008; Radi et al. 2010), antiparasitic (Garg et al. 1973; Rathelot et al. 2002), antiviral (Comber et al. 1991; Manfredini et al. 1992; Storer et al. 1999; Johansson et al. 2002; Rostom et al. 2003; Sweeney et al. 2008), analgesics (Menozzi et al. 1997; Pinto et al. 1999) antiglycemic agents (Bauer et al. 1968; Kees et al. 1996; Bebernitz et al. 2001) and even as anti-inflammatory agents (Bekhit et al. 2003; Bekhit et al. 2005; Bekhit et al. 2006; Burguete et al. 2007).

Some of the specific examples include curcumin-derived pyrazoles, which inhibit secretion of amyloid $\beta$ (A$\beta$) responsible for Alzeheimers disease (Narlawar et al. 2007, 2008). Others are *N*-acetyl pyrazole and pyrazolothiazolone as antivirals (Shen et al. 2004a; El-Sabbagh et al. 2009), pyrazol-thioketone and aryl/cyclohexyl-thio substituted pyrazoles as antimicrobials (Chande et al. 1999; Manikannan et al. 2010) and o-hydroxy-phenylpyrazoles as analgesics (Pinto et al. 1999). Further examples are triarylpyrazoles (Stauffer et al. 2000, 2001) and pyrazolopyrimidines (Zhou et al. 2007) reported as estrogen receptor (ER) antagonists.

With pyrazoles showing therapeutic properties as briefly mentioned above, and with examples of metals complexes having therapeutic value such as *cis*-dichlorodiammineplatinum(II) (cisplatin) used to treat various cancers, it was not long before pyrazole-based complexes were also prepared and investigated for their therapeutic values. One of the first pyrazole complexes to be investigated was *cis*-dichlorobis(pyrazole)platinum(II) (**2**) that showed anticancer properties (Sakai et al. 2000). Several pyrazole and pyrazolyl complexes have since been prepared and probed for their therapeutic action across a spectrum of diseases such as cancer (Komeda et al. 2000; Al-Allaf and Rashan 2001; Wheate et al. 2001; Sakai et al. 2000; Pettinari et al. 2006; Keter et al. 2008; Casas et al. 2008; Segapelo et al. 2009; Zhang et al. 2010; Mosoarca et al. 2011), antimicrobials and antifungal (Al-Allaf et al. 1993; Nomiya et al. 2000; Mahmud et al. 2001; Fang et al. 2003; Tharmaraj et al. 2009; Sharma et al. 2009; Negm et al. 2010; Kulkarni and Revankar 2011) and as anti-viral agents (Kratz et al. 1992; Fonteh et al. 2009). For these reasons there is growing pharmacological interest in pyrazole-derived compounds given that the pyrazole motif makes up the core structure of numerous biologically active compounds (Elguero et al. 2002).

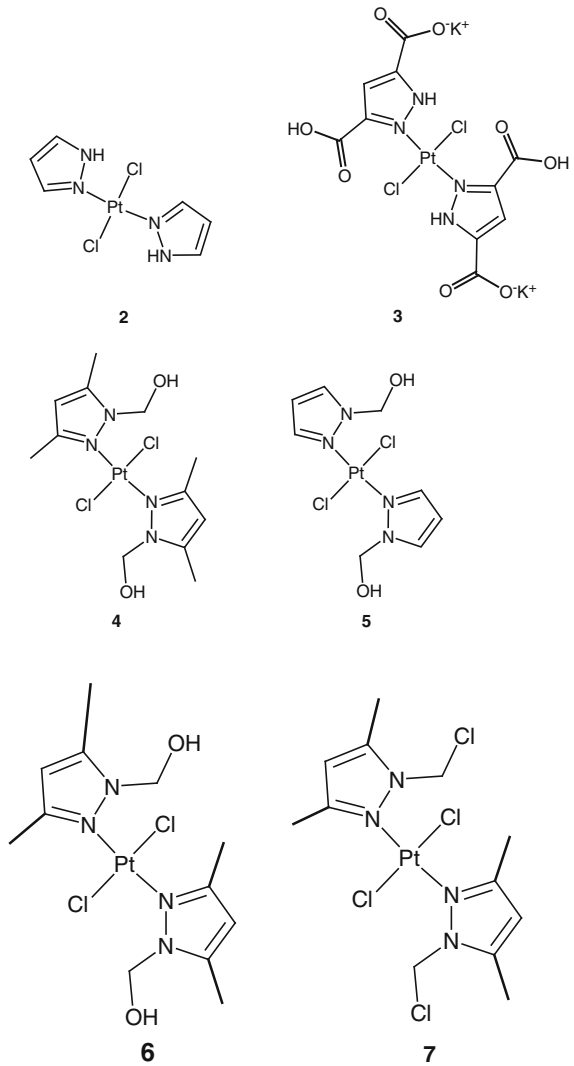
This mini-review is therefore meant to demonstrate that complexes of pyrazole-based ligands hold promise in medicine. Suffice it to say that complexes of nitrogen-donor ligands in general have shown interesting or potential biological activities for different ailments ranging from cancer to bacterial and parasitic infections. It has been amply demonstrated that a metal fragment tend to add value to an already active organic fragment (ligand). This, no doubt, is due to the ability of metals to influence the electronics of the resultant complexes when bound to such organic fragments; thereby improving the therapeutic value of the overall compound. Compared to other nitrogen-donor metal complexes, pyrazole and pyrazolyl metal complexes have been less extensively used in medicine. The following sections would be used to illustrate the growth in the use of pyrazole-based complexes as anticancer, antibacterials & antiparasitic and anti-viral agents; and hence the potential that pyrazoles and their derivatives, either by themselves or on complexes have in medical applications.

## Pyrazole complexes in medicine

### Cancer

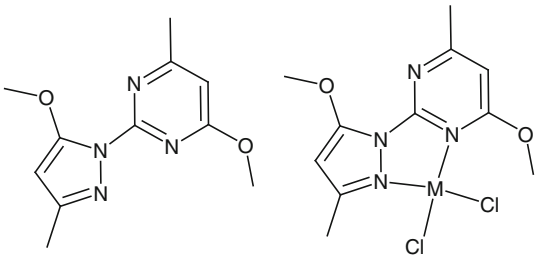
Interest in complexes in cancer can be traced back to the serendipitous discovery of cisplatin by Rosenberg et al. (1965, 1969) as an anticancer agent. In spite of its excellent activity against various cancers, its toxicity is a constant worry. For this reason researchers continue to look for better compounds that are less toxic. As such many second generation compounds, mimics to cisplatin, have been prepared. They include carboplatin (Harrap 1985; Kelland et al. 1999), iproplatin (Braddock et al. 1975; Tobe and Khokhar 1977) and oxaliplatin (Kidani et al. 1980; Graham et al. 2004). Sadly these compounds, too, show some toxicity; hence the search continues.

Pyrazoles in cancer were first introduced by Sakai et al. (2000) when they reported anticancer activities of dichloro-bis(pyrazole)platinum(II), $PtCl_2(pzH)_2$ (**2**), and dichloro-bis(pyrazoledicarboxylic-acid)platinum(II) dipotassium salt, $PtCl_2(3\text{-}CO_2H,5\text{-}CO_2KpzH)_2$ (**3**) against human colorectal cell lines (DLD-1, HCT15, HT29) and a human gastric cell line (AGS). While compound **3** was ineffective, **2** was active against the four cell lines mentioned above. The activity of **2** ($IC_{50}$ values: DLD-1, 2.76 μM; HCT15, 6.5 μM; HT29, 2.1 μM; AGS, 2.84 μM) was similar to that of cisplatin (DLD-1, 2.31 μM; HCT15, 2.5 μM; HT29, 1.2 μM; AGS, 2.13 μM) (Sakai et al. 2000). Compound **2** was also tested against L1210 murine leukemia cells with an $IC_{50}$ of 4.6 μM compared to cisplatin (1.2 μM) and carboplatin (11.2 μM) (Ciesielska et al. 2006). We have also tested **2** and $PtCl_2(3,5\text{-}Me_2pzH)$ (**4**) against human cervical epitheloid carcinoma (HeLa and CaSki) and leukemia (Jurkat) cells and found that they induce caspase-3 and DNA fragmentation (Keter et al. 2008). Other closely related compounds that have anticancer activity: are *cis*-dichloro-bis-(*N*-hydroxymethylpyrazole-$\kappa N^2$)platinum(II), $PtCl_2(Hmpz)_2$ (**5**), *cis*-dichloro-bis-(*N*-hydroxymethyl-3,5-dimethylpyrazole-$\kappa N^2$)platinum(II), $PtCl_2(HM\text{-}3,5\text{-}dmpz)_2$ (**6**) and *cis*-dichloro-bis-(*N*-chloromethyl-3,5-dimethylpyrazole-$\kappa N^2$)platinum(II), $PtCl_2(Clmpz)_2$ (**7**) that are cytotoxic to L1210 murine leukemia cells (Ciesielska et al. 2006). The recorded $ED_{50}$ values are 4.1, 3.5 and 4.4 μM for compounds **5**, **6** and **7** respectively. These activities are lower compared to cisplatin (1.2 μM) but better than carboplatin (11.2 μM) on the same cell line (Ciesielska et al. 2006). Interest in this class of pyrazolyl complexes, though, lies in the way they act against cancer cell lines. Whereas their cytotoxicities are similar, **2**, **5** and **6** induce DNA laddering after a 3 h drug exposure period and after 24 h post-drug incubation; while **7** and cisplatin only induce the laddering after a total of 48 h post-drug incubation. Given that DNA fragmentation is the hallmark of apoptosis, it therefore follows that **2**, **5** and **6** induce apoptosis earlier than **7** and cisplatin (Ciesielska et al. 2006).



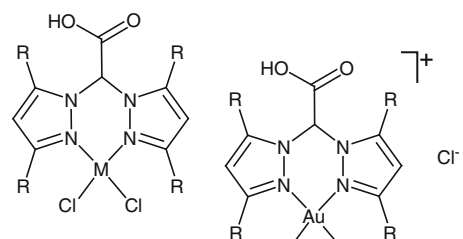

Mepirizole (**8**), an active pyramidino pyrazole, used as an analgesic and anti-inflammatory agent (Takabatake et al. 1970), has also been used to prepare palladium(II) (**9**) and platinum(II) (**10**) complexes by Onoa et al. (1999). It is clear that these researchers took advantage of mepirizole's biological property by using

it to make **9** and **10** as cisplatin mimics. However, **9** and **10** were inactive against cervical cancer cells, HeLa (Onoa et al. 1999). A series of studies involving quantification of non-bound and bound metal pointed to the inability of **9** and **10** to cross the cell membrane, hence poor activities observed by Onoa et al. (1999).



**8** M = Pd (**9**); Pt (**10**)

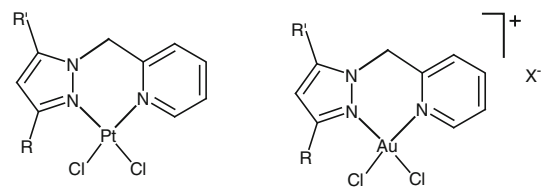
Another set of compounds are the bis(pyrazolyl)-palladium(II) (**11** and **12**), platinum(II) (**13** and **14**) and gold(III) complexes (**15** and **16**) reported by us (Keter et al. 2009b). The appeal of gold complexes comes from recent indication of their potential as anticancer agents. However, gold(III) complexes as anticancer agents are much less investigated owing to its instability and tendency to readily undergo reduction in physiological conditions. It is believed that strongly binding ligands; preferably those featuring hard base donors are needed to make gold(III) anticancer agents. Thus, our choice of bis(pyrazolyl)acetic compounds as ligands to make gold(III) complexes was based on this believe. Unfortunately **11**–**16** were between 14 and 71 times less active (1.1–5.1 mM) than cisplatin (0.07 mM) when tested against Chinese hamster ovary (CHO) cells (Keter et al. 2009b). One similarity drawn from our work (Keter et al. 2009b) and that reported by Sakai et al. (2000) is that the carboxylic group of the bis(pyrazolyl)acetic ligand reduce the activities of these complexes. It has been suggested that the bulkiness of the carboxylic moiety and its contribution to the overall reduction of the electron density of the pyrazole may be responsible for the low activity (Ciesielska et al. 2006).



R = H, M = Pd (**11**)
R = Me, M = Pd (**12**)
R = H, M = Pt (**13**)
R = Me, M = Pt (**14**)

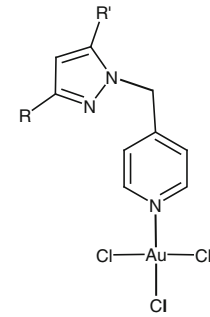
R = H (**15**)
R = Me (**16**)

Noteworthy is the fact that the bis(pyrazolyl) acetic acid are able to stabilize palladium(II) and platinum(II) complexes long enough to allow for the study of their substitution reactions with cysteine. Whereas the same is true for their gold(III) analogues, the resultant substitution products undergo facile reduction (Keter et al. 2009b). This is probably one of the reasons for lack of activity of the bis(pyrazolyl)gold(III) complexes, even though there was no correlation between the kinetics and the biological data (Keter et al. 2009b). Further efforts to try and explore pyrazoles as stabilizing ligands, particularly for gold(III), led to isolation of platinum(II) and gold(III) complexes of (pyrazolylmethyl)pyridines (**17**–**25**) (Segapelo et al. 2009). The multidentate nature of these pyrazolyl compounds offers plausible route to preparing stable complexes and also lead to square planar geometries. In this group of complexes, **23** and **25** had relatively good activities against HeLa cells (3.8–8.9 μM). However, they were found to be toxic to normal cells pointing to indiscriminate killing of cells by these compounds (Segapelo et al. 2009).



R = Me, R' = Me (**17**)
R = Ph, R' = Ph (**18**)
R = *t*Bu, R' = *t*Bu (**19**)
R = *p*-tol, R = H (**20**)

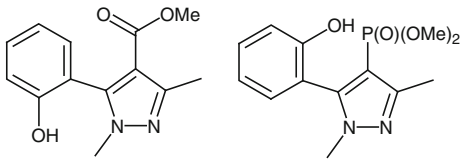
R = Me, R' = Me X = $[AuCl_4]^-$(**21**)
R = Ph, R' = Ph X= $Cl^-$(**22**)
R = *p*-tol, R = H X= $[AuCl_4]^-$(**23**)



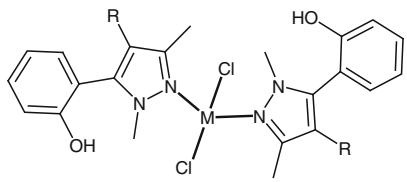
R = Me, R' = Me (**24**)
R = Ph, R' = Ph (**25**)

In another study Budzisz et al. (2004a) reported the use of phosphonic-based pyrazoles, 5-(2-hydroxyphenyl)-1,3-dimethyl-4-(dimethoxy)phosphonyl-1H]-pyrazole (**26**) and 5-(-2-hydroxyphenyl)-1,3-dimethyl-4-methoxycarbanyl-1H]-2-pyrazole (**27**), to prepare palladium(II), platinum(II) and copper(II)

complexes (**28**–**33**). Complexes **28**–**33** were investigated for their potential anticancer activities. The phosphonyl moieties in the **28**–**33** were intended to impart alkylating ability to the complexes, whilst the pyrazole moiety were meant to offer selectivity. The complexes were obtained by reacting **26** and **27** with $K_2PtCl_4$ or $PdCl_2(PhCN)_2$. Even though no solid state structure was given, the spectroscopic data pointed to isolation of the *cis*- and *trans*-complexes.

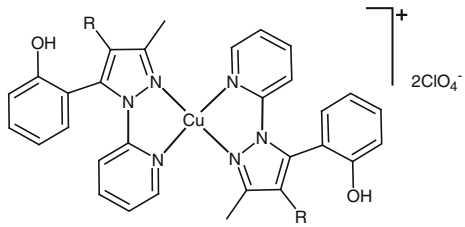



**26** **27**




R = $CO_2Me$, $CO_2Me$; M = Pd (**28**)
R = $CO_2Me$, $CO_2Me$; M = Pt (**29**)
R = $P(O)(OMe)_2$, $P(O)(OMe)_2$; M = Pd (**30**)
R = $P(O)(OMe)_2$, $P(O)(OMe)_2$; M = Pt (**31**)

It is evident from the preussman test results, a tool to investigate the alkylating abilities, that compound **29** was more alkylating than the reference compound, cisplatin (Budzisz et al. 2004b). Disappointingly though, is the fact that all these phosphonic-based pyrazoles complexes were less active than cisplatin (0.8 μM) in leukemia HL-60 and NALM-6 cells, where the best activity was shown by compound **29** (8.9 and 25.7 μM for NALM-6 and HL-60 cells, respectively). Nevertheless, **28**–**33** induced caspase-3 at different rates; and binds DNA preferentially at the GC sequence, but with low affinity. More importantly is the fact that these compounds, **29** in particular, were not toxic to non-cancerogenic HUVEC cells ($IC_{50}$ = 708.7 μM) compared to cisplatin ($IC_{50}$ = 96.1 μM) indicating its potential non-toxicity to normal cells (Budzisz et al. 2004b). Other examples include the trigonal bipyramidal copper complexes of pyrazole-phosphonic ligands such as copper complexes of 5-(2-hydroxyphenyl)-3-methyl-1-(2-pyridylo)-1H-pyrazole-4-carboxylic acid methyl ester (**32**) and 5-(2-hydroxyphenyl)-3-methyl-1-(2-pyridylo)-1H-pyrazole-4-phosphonic acid (**33**) (Budzisz et al. 2009). Complex **32** exhibited better activity against leukemia and melanoma, respectively (~6.5 μM in HL60 cells and ~8 μM in WM-115 cells) than its analogues **28** (~134 μM in HL60 cells; ~484 μM in WM cells) and **29** (~58 μM in HL60 cells; ~77 μM in WM cells). However, **32** was no better than carboplatin (4.3 μM) and cisplatin (0.8 μM) in HL60 cells, albeit better than the two in melanoma WM cells (carboplatin, 422.2 μM; cisplatin, 18.2 μM) (Budzisz et al. 2009).



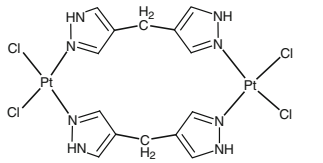

R = $CO_2Me$ (**32**);
R = $P(O)(OMe)_2$ (**33**)

Other relevant compounds include the dipyrazolylmethane-based (dpzm) platinum(II) complex, $\beta$-$[PtCl_2(\mu\text{-dpzm})_2PtCl_2]$ (**34**), reported by Broomhead et al. (1992). Apart from the DNA binding abilities of **34**, it showed activity against P338 murine leukemia cells (Broomhead et al. 1993); and unlike mononuclear complexes such as *cis*- and *trans*-platin, **34** is thought to form unique types of Pt-DNA adducts. Later on Broomhead et al. (1998) used dpzm to prepare several complexes of general formulae $[MCl_2(dpzm)]_n$ (M = Zn, Cu) (**35**–**36**) and $[MCl_2(dpzm)_2]_n$ (M = Mn, Fe, Co, Ni, Cu) (**37**–**41**) of which **40** and **41** showed activity against P338 murine leukemia and DNA binding abilities. Furthermore, dpzm ligands have been used to modify cisplatin to give cationic multinuclear platinum complexes *trans*-$[\{Pt(NH_3)_2Cl\}_2\text{-}\mu\text{-dpzm}]Cl_2$ (**42**) and *trans*-$[trans\text{-}\{Pt(NH_3)_2Cl\}_2\{trans\text{-}[Pt(NH_3)_2(\mu\text{-dpzm})_2]\}]Cl_4$ (**43**) (Wheate et al. 2001). Both complexes show activity in L1210 murine leukaemia cells ($IC_{50}$ = 3.8 and 2.5 μM, respectively) and form very high levels of DNA interstrand cross-links in vitro; a factor adduced to the rigid nature of dpzm linking ligand that inhibits formation of intra-strand adducts observed for cisplatin (Wheate et al. 2001). Wheate and Collins (2003) have authored an excellent review on multinuclear platinum complexes based on dpzm and the reader is encouraged to refer to it.

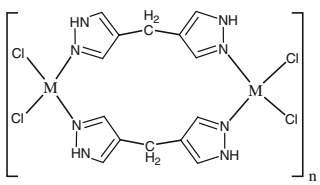
New Schiff-based pyrazolyl copper(II) complexes, chloro[*N*-(2-hydroxy-3,5-dichloride-benzyl-2-pyrazo

lethyl)iminate]copper(II) (**44**) and chloro[*N*-(2-hydroxy-3,5-diiodine-benzyl-2-pyrazolethyl)iminate] copper(II) (**45**) complexes were recently reported (Gama et al. 2011) to have shown therapeutic action against prostate (PC-3), breast (MCF-7) and ovarian (A2780 and A2780cisR) cancer cells. The $IC_{50}$ values of **44** (PC-3, 45 μM; MCF-7, 31 μM; A2780, 20 μM; A2780cisR, 28 μM) and **45** (PC-3, 39 μM; MCF-7, 26 μM; A2780, 13 μM; A2780cisR, 18 μM) were comparable to those of cisplatin (PC-3, 51 μM; MCF-7, 28 μM; A2780cisR, 17 μM) after 72 h of treatment, except in the case of A2780 cells (1.9 μM). In addition, **44** and **45** induced DNA cleavage in the presence of ascorbic acid. Overall, **45** was more active than **44** and is attributed to its enhanced stabilization as a result of Cu(II)/Cu(I) redox potential presumably imparted by the halogen substituent groups because of their π-donating effect (Gama et al. 2011).

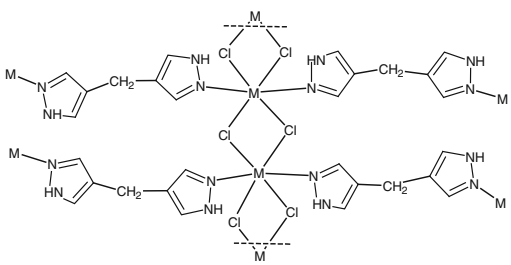
It is worth mentioning that despite all the attempts to find new drugs such efforts have not been very successful, however considerable gains have been made that has led to better understanding of the functionality of this class of compounds. As such, to date, cisplatin (Platinol®), carboplatin (Paraplatin®) and oxaliplatin (Eloxatin®), remain the most commonly used anticancer drugs. Platinol and Paraplatin are known to be effective against ovarian, bladder, lung, esophageal, breast, and cervical cancers amongst many other cancers. On the other hand, Eloxatin is used in combination with other drugs, such as fluorouracil, to treat metastatic rectal cancer. They remain useful drugs in the market despite their toxicity levels.



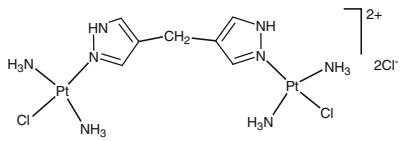
**34**



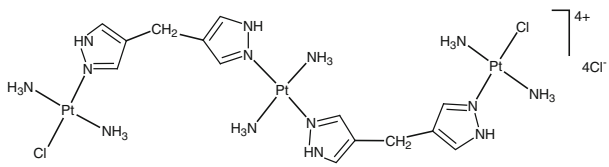
M = Zn (**35**), Cu (**36**)



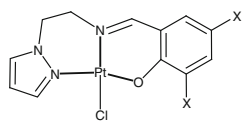
M = Mn (**37**), Fe (**38**), Co (**39**), Ni (**40**), Cu (**41**)



**42**



**43**

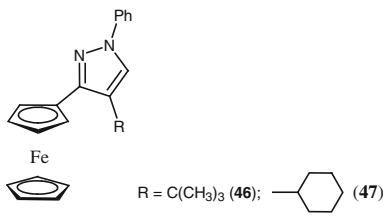


X = Cl (**44**), I (**45**)

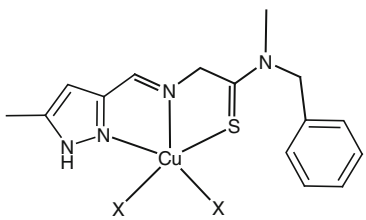
## Antiparasites and antibacterials

It is no doubt that in the 21st century we have seen signs of strains that are developing resistance to existing antibacterial concoctions, e.g. ciprofloxacin, nobobiocin and counamins. These strains include *Staphylococcus aureas*, S*treptococcus pneumonia* and *Enterococci*. Thus efforts to find alternative antibacterial agents to overcome the growing resistance problems are necessary. Amongst the compounds reported as a result of these efforts are the ferrocenylpyrazoles that show superb antibacterial activity against Gram positive bacteria (Damljanovic et al.

2009). By coupling pyrazoles, which are known to have antimicrobial activity (Kucukguzel et al. 2000; Genin et al. 2000b; Adnan and Abdel-Aziem 2004; Bekhit et al. 2005) with ferrocene moieties known for its advantage to cross the cell membrane (Dombrowski et al. 1986), compounds **46** and **47** were isolated and shown to be active against an array of bacteria. The activities of **46** and **47** compare well with the reference compounds tetracycline and nistatine. Design of such compounds was buoyed by positive results obtained when ferrocene was derivatised with chloroquine to form ferrochloroquine, which is active against the chloroquine-resistant strain of *Plasmodium falciparum* (Biot et al. 1997). These ferrocenyl pyrazoles were prepared by condensation of acetylferrocene with phenylhydrazine. Cyclization process completes the process to form the end product, **46** and **47**.

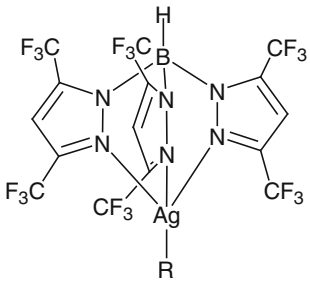



Interestingly in an attempt to improve antibacterial activities of thiosemicarbazone-based compounds, pyrazole moieties have been incorporated. A classical example are complexes of the general formula $[Cu(HMPz_4BM)X_2]$ (X = Cl, $NO_3$, Br, $BF_4$) (**48**–**51**) reported by Sau et al. (2003). Two of these compounds, **48** and **49**, showed antibacterial activity against Gram-positive *Staphylococcus aureas* with 97 and 96% growth inhibitions, respectively at 500 μg/ml. The lack of activities for **50** and **51** was attributed to their ease of solvolysis compared to **48** and **49**; and is supported by high cathodic peak potentials, which is associated with an irreversible process (Sau et al. 2003).




X = Cl (**48**), $NO_3$ (**49**), Br (**50**), $BF_4$ (**51**)

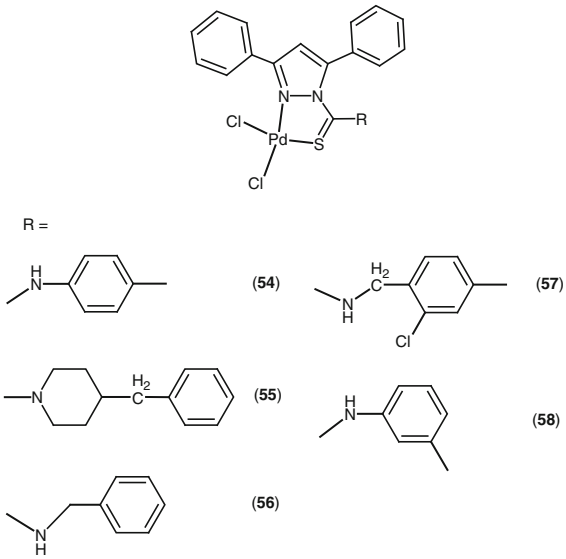
Silver(I) pyrazolyl compounds have also been reported because of their attractiveness as antimicrobial agents. Silver compounds are generally known to have antimicrobial properties and exert their activities through interaction with DNA, reacting with thiol groups in proteins and interfering with electron transport (Russell and Hugo 1994). The highly fluorinated tris(pyrazolyl)borate silver complexes, $[HB(3,5\text{-}(CF_3)_2pz)_3]Ag(OSMe_2)]$ (**52**) and $[HB(3,5\text{-}(CF_3)_2pz)_3]Ag(thf)]$ (**53**) were reported by Dias et al. (2006) to show activities against *Staphylococcus aureas* with minimum inhibitory concentrations of approximately six times less than the reference compound Ag(I) sulfadiazine (16 μg/ml). The authors postulated that the activities are due to the ability of $HB(3,5\text{-}(CF_3)_2pz)_3$ to make bioavailability of silver ions optimal. This is probably true owing to the highly electron deficient nature of $HB(3,5\text{-}(CF_3)_2pz)_3$ brought about by the presence of $CF_3$ groups; which in turn creates a highly electrophilic silver complex, hence silver remaining in an optimal ion state for microbial activity.




R = $Me_2SO$ (**52**), thf (**53**)

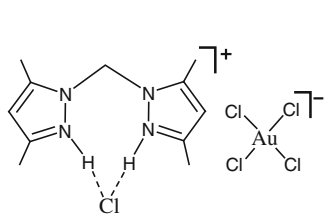
Another area of medicinal application for pyrazole and pyrazolyl compounds is as antiparasitics. Budakoti et al. (2007) reported a series of pyrazolyl palladium(II) complexes that exhibit antiamoebic activity. It is believed that amoeba infection comes third in the ranking of parasitic infections, thereby posing a great danger to the human populace. It is against this backdrop that new antiparasitic therapies are sought after. In their study Budakoti et al. (2007) described the syntheses of palladium compounds based on a series of 1-*N* substituted thiocarbonyl-3,5-diphenyl-2-pyrazolines, of which five (**54**–**58**) had good activities. Coordination of the ligands to palladium(II) ion led to improved efficacy, with $IC_{50}$ values of 0.05, 0.4, 0.7, 1.24 and 1.82 μM for **54**–**58,** respectively compared to the corresponding ligands ($IC_{50}$ = 0.38, 1.6, 2.8, 11 and 10.7 μM). Notably, the palladium precursor used,

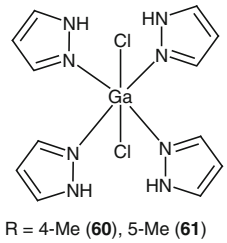
$[PdCl_2(dmso)_2]$, had low activity (8.15 μM); pointing to the synergistic effect of the pyrazolyl ligands and palladium in complexes **54**–**58**.




## Antiviral agents

Whereas there are several examples of pyrazole-derived organic compounds reported to have anti-viral action, as exemplified by a number of registered patents and research papers (Carabateas and Diana 1980; Pancic et al. 1981; Ding et al. 1989; Manfredini et al. 1992; La Colla et al. 1996; Shen et al. 2004b; Bravi et al. 2005; Shipps Jr et al. 2006a; Shipps Jr et al. 2006b; Ouyang et al. 2008; Li et al. 2010, 2011; Shih et al. 2010; Wu et al. 2011), there are few examples of their pyrazolyl metallo-antivirals. One of the few known metallo-antivirals is tetra-chloro-bis(3,5-dimethylpyrazolyl)methanegold(III) chloride, $[3,5\text{-}Me_2bpzaH_2][AuCl_4]Cl$, (**59**) reported by us (Fonteh et al. 2009). Compound **59** showed activity against HIV-1 reverse transcriptase (RT) and protease (PR). This compound is a salt containing a doubly protonated pyrazolyl unit, $[3,5\text{-}Me_2bpzaH_2]$, with $AuCl_4^-$ and $Cl^-$ as the counterions. What is remarkable about this complex is that it inhibits both RT and PR enzymes at concentration between 5 and 250 μM, and was non-toxic to normal cells at its inhibitory concentrations (Fonteh et al. 2009). Given that PR and RT are both targets for anti-HIV regiments, the ability of this compound to target both indicated dual functionality. Furthermore, the fact that $HAuCl_4.4H_2O$, used to prepare the gold complexes, was not active confirmed that the dual activity is because of the effect of the bis(pyrazolyl)methane on tetrachloroaurate.




Another metal that forms pyrazolyl metallodrugs is gallium. Gallium compounds, known in medicine for both diagnostic and therapeutic properties, have also been investigated as antivirals. For example $[GaCl_2(4\text{-}MepzH)_4]GaCl_4$ (**60**) and $[GaCl_2(5\text{-}MepzH)_4]GaCl_4$ (**61**) (4-MepzH = 4-methylpyrazole, 5-MepzH = 5-methylpyrazole) are known to have anti-HIV activity (Kratz et al.1992). These octahedral compounds were obtained by reacting chlorogallate salts with the respective pyrazoles. The anti-HIV analysis showed that compounds **60** and **61** had moderate activities, 108 and 231 μM, respectively on CEM cell line. However, their low therapeutic indices, 1.11 and 1.52 for **60** and **61**, respectively suggested poor selectivity compared to AZT, which has a therapeutic index of 1027 (Kratz et al. 1992).

## Summary

The main objective of this perspective is to bring attention to pyrazole-based metal complexes and their potential in drug development and medicine in general. It is evident that pyrazole derivatives have been investigated for a number of ailments as highlighted in the first section of this review. This is not only due to the fact that pyrazole is similar to imidazole, a biologically relevant compound, but also that pyrazoles are relatively easy to synthesize and can be fine-tuned to achieve desired electronic and steric effects. Thus, pyrazole and pyrazolyl compounds are gaining attention, inter alia, as antiviral, anticancer and antimicrobial agents. However, the same cannot be said about pyrazole and pyrazolyl metal complexes and thus the need to pursue this further. Such efforts

could include isolating complexes of known therapeutic pyrazole and pyrazolyl ligands.

There is no doubt that investigation of pyrazole-based metal complexes for their therapeutic properties is in its infancy and will continue to grow. It would be interesting to see how this area of metallodrugs discovery will be like 10 years from now if continued attention is given to this group of compounds.

**Acknowledgment** The authors would like to acknowledge Mintek and University of Johannesburg for support for some of the work cited in this review.

## References

Abunada NM, Hassaneen HM, Kandile NG, Miqdad OA (2008) Synthesis and antimicrobial activity of some new pyrazole, fused pyrazolo[3, 4-d]-pyrimidine and Pyrazolo[4, 3-e][1, 2, 4]-triazolo[1, 5-c]pyrimidine derivatives. Molecules 13: 1501–1517

Adnan AB, Abdel-Aziem T (2004) Design, synthesis and biological evaluation of some pyrazole derivatives as anti-inflammatory-antimicrobial agents. Bioorg Med Chem 12: 1935–1945

Aiello E, Aiello S, Mingoia F, Bacchi A, Pelizzi G, Musiu C, Setzu MG, Pani A, La Colla P, Marongiu ME (2000) Synthesis and antimicrobial activity of new 3-(1-R-3(5)-methyl-4-nitroso-1H-5(3)-pyrazolyl)-5-methylisoxazoles. Bioorg Med Chem 8:2719–2728

Akbas E, Berber I (2005) Antibacterial and antifungal activities of new pyrazolo[3, 4-d]pyridazin derivatives. Eur J Med Chem 40:401–405

Al-Allaf TAK, Rashan LJ (2001) *Cis*- and *trans*-platinum and palladium complexes: a comparative study review as antitumor agents. Boll Chim Farm 140:205–210

Al-Allaf TAK, Al-Bayati RH, Khalaf SH (1993) Synthesis and spectroscopic studies on organotin(IV) complexes of some pyrazoles and pyrazol-5-ones and their antibacterial activity. Appl Organomet Chem 7:635–640

Bauer VJ, Dalalian HP, Fanshawe WJ, Safir SR, Tocus EC, Boshart CR (1968) 4-[3(5)-pyrazolyl]pyridinium salts. A new class of hypoglycemic agents. J Med Chem 11: 981–984

Bebernitz GR, Argentieri G, Battle B, Brennan C, Balkan B, Burkey BF, Eckhardt M, Gao J, Kapa P, Strohschein RJ, Schuster HF, Wilson M, Xu DD (2001) The effect of 1, 3-diaryl-[1H]-pyrazole-4-acetamides on glucose utilization in ob/ob mice. J Med Chem 44:2601–2611

Bekhit AA, Fahmy HTY, Rostom SAF, Baraka AM (2003) Design and synthesis of some substituted 1H-pyrazolyl-thiazolo[4,5-d]pyrimidines as anti-inflammatory-antimicrobial agents. Eur J Med Chem 38:27–36

Bekhit AA, Ashour HMA, Guemei AA (2005) Novel pyrazole derivatives as potential promising anti-inflammatory antimicrobial agents. Arch Pharm 338:167–174

Bekhit AA, Abdel-Rahman HM, Guemei AA (2006) Synthesis and biological evaluation of some hydroxypyrazole derivatives as anti-inflammatory-antimicrobial agents. Archiv der Pharmazie 339:81–87

Bildirici I, Sener A, Tozlu I (2007) Further derivatives of 4-benzoyl-1, 5-diphenyl-1Hpyrazole-3-carboxylic acid and their antibacterial activities. Med Chem Res 16: 418–426

Biot IC, Glorian G, Maciejewski L, Brocard L, Domarle O, Blampaim G, Millet P, Georges AJ, Abesolo H, Dive O, Lebibi J (1997) Synthesis and antimalarial activity in vitro and in vivo of a new ferrocene–chloroquine analogue. J Med Chem 40:3715–3718

Blomstrand R (1972) In: Akeson A, Ehrenberg A (eds) Structure and function of oxidation–reduction enzymes. Pergamon, Oxford, pp 667–679

Blomstrand R, Ostling-Wintzell H, Lof A, McMartin K, Tolf B, Hedstrom K (1979) Pyrazoles as inhibitors of alcohol oxidation and as important tools in alcohol research: an approach to therapy against methanol poisoning. Proc Natl Acad Sci USA 76:3499–3503

Braddock PD, Connors TA, Jones M, Khokhar AR, Melzack DH, Tobe ML (1975) Structure and activity relationships of platinum complexes with anti-tumour activity. Chem-Biol Interact 11:145–161

Bravi G, Corfield JA, Grimes RM, Guidetti R, Lovegrove VLH, Mordaunt JE, Shah P, Slater MJ (2005) 4-Carboxpyrazole derivatives useful as antivirals agents. Pat. No. WO/2005/092863

Broomhead JA, Rendina I, Sterns M (1992) Dinuclear complexes of platinum with the 4,4′-dipyrazolylmethane ligand. Synthesis, characterization, and x-ray crystal structure of.gamma.-bis(4,4′-dipyrazolylmethane-*N*,*N*′)bis[dichloroplatinum(II)]-*N*,*N*-dimethylformamide (1/2) and related complexes. Inorg Chem 31:1880–1889

Broomhead JA, Rendina I, Webster LK (1993) Dinuclear complexes of platinum having anticancer properties. DNA-binding studies and biological activity of Bis(4,4′-dipyrazolylmethane-N,N′)-bis[dichloroplatinum(II)] and related complexes. J Inorg Biochem 49:221–234

Broomhead JA, Camm G, Sterns M, Webster L (1998) Dinuclear complexes of first transition series metals with 4,4′-dipyrazolylmethane: characterisation, DNA binding and anticancer properties. Inorg Chim Acta 271:151–159

Budakoti A, Abid M, Azam A (2007) Syntheses, characterization and in vitro antiamoebic activity of new Pd(II) complexes with 1-*N*-substituted thiocarbamoyl-3,5-diphenyl-2-pyrazoline derivatives. Eur J Med Chem 42:544–551

Budzisz E, Malecka M, Nawrot B (2004a) Synthesis and structure of highly substituted pyrazole ligands and their complexes with platinum(II) and palladium(II) metal ions. Tetrahedron 60:1749–1759

Budzisz E, Krajewska U, Rozalski M, Szulawska A, Czyz M, Nawrot B (2004b) Biological evaluation of novel Pt(II) and Pd(II) complexes with pyrazole-containing ligands. Eur J Pharmacol 502:59–65

Budzisz E, Miernicka M, Lorenz I-P, Mayer P, Krajewska U, Rozalski M (2009) Synthesis and X-ray structure of platinum(II), palladium(II) and copper(II) complexes with pyridine–pyrazole ligands: influence of ligands' structure on cytotoxic activity. Polyhedron 28:637–645

Burguete A, Pontiki E, Hadjipavlou-Litina D, Villar R, Vicente E, Solano B, Ancizu S, Perez-Silanes S, Aldana I, Monge A

(2007) Synthesis and anti-inflammatory/antioxidant activities of some new ring substituted 3-phenyl-1-(1,4-di-N-oxide quinoxalin-2-yl)-2-propen-1-one derivatives and of their 4,5-dihydro-(1H)-pyrazole analogues. Bioorg Med Chem Lett 17:6439–6443

Carabateas PM, Diana GD (1980) Antiviral arylenedioxyalkyl substituted pyrazoles. Pat. No. 06/008412

Casas JS, Castellano EE, Ellena J, García-Tasende MS, Pérez-Parallé ML, Sánchez A, Sánchez-González A, Sordo J, Touceda A (2008) New Pd(II) and Pt(II) complexes with N,S-chelated pyrazolonate ligands: molecular and supramolecular structure and preliminary study of their in vitro antitumoral activity. J Inorg Biochem 102:33–45

Chande MS, Thakkar NV, Patil DV (1999) Synthesis and antimicrobial activity of bis[6-phenyl-4-methyl-3-substituted-pyrazo[4,5-d]pyrazol-1-yl]thioketones. Drug Res 56:207–210

Ciesielska E, Szulawska A, Studzian K, Ochocki J, Malinowska K, Kik K, Szmigiero L (2006) Comparative studies on the mechanism of cytotoxic action of novel platinum II complexes with pyrazole ligands. J Inorg Biochem 100: 1579–1585

Comber RN, Gray RJ, Secrist JA III (1991) Acyclic analogues of pyrazofurin: syntheses and antiviral evaluation. Carbohydr Res 216:441–452

Dahlbom R, Tolf BR, Akeson A, Lundquist G, Theorell H (1974) On the inhibitory power of some further pyrazole derivatives of horse liver alcohol dehydrogenase. Biochem Biophys Res Commun 57:549–5353

Damljanovic I, Vukicevic M, Radulovic N, Palic R, Ellmerer E, Ratkovic Z, Joksovic MD, Vukicevic RD (2009) Synthesis and antimicrobial activity of some new pyrazole derivatives containing a ferrocene unit. Bioorg Med Chem Lett 19:1093–1096

Di Parsia MT, Suarez C, Vitolo MJ, Marquez VE, Beyer B, Urbina C, Hurtado I (1981) Synthesis and study of the potential antiallergic activity of some pyrazole derivatives. J Med Chem 24:117–119

Dias HVR, Batdorf KH, Fianchini M, Diyabalanage HVK, Carnahan S, Mulcahy R, Rabiee A, Nelson K, van Waasbergen LG (2006) Antimicrobial properties of highly fluorinated silver(I) tris(pyrazolyl)borates. J Inorg Biochem 100:158–160

Ding L, Grehn L, De Clercq E, Andrei G, Snoeck R, Balzarini J, Fransson B, Ragnarsson U (1989) Synthesis and antiviral activity of three pyrazole analogues of distamycin A. Acta Chem Scand (Copenhagen, Denmark) 48:498–505

Dombrowski KE, Baldwin W, Sheats JE (1986) Metallocenes in biochemistry, microbiology & medicine. J Organomet Chem 302:281–306

Duivenvoorden WCM, Liu Y-N, Schatte G, Kraatz H-B (2005) Synthesis of redox-active ferrocene pyrazole conjugates and their cytotoxicity in human mammary adenocarcinoma MCF-7 cells. Inorg Chim Acta 358:3183–3189

Eklund H, Nordström B, Zeppezauer E, Söderlund G, Ohlsson I, Boiwe T, Söderberg BO, Tapia O, Brändén CI, Akeson A (1976) Three-dimensional structure of horse liver alcohol dehydrogenase at 2–4 Å resolution. J Mol Biol 102:27–59

Eklund H, Samama J-P, Wallen L (1982) Pyrazole binding in crystalline binary and ternary complexes with liver alcohol dehydrogenase. Biochemistry 21:4858–4866

El-Gaby MSA, Atalla AA, Gaber AM, Al-Wahab KAA (2000) Studies on aminopyrazoles: antibacterial activity of some novel pyrazolo[1, 5-a]pyrimidines containing sulfonamido moieties. Farmaco 55:596–602

Elguero J, Goya P, Jagerovic N, Silva AMS (2002) Pyrazoles as drugs: facts and fantasies. Targets Heterocycl Syst 6: 52–98

El-Sabbagh OI, Baraka MM, Ibrahim SM, Pannecouque C, Andrei G, Snoeck R, Balzarini J, Rashad AA (2009) Synthesis and antiviral activity of new pyrazole and thiazole derivatives. Eur J Med Chem 44:3746–3753

Fang J, Jin Z, Li Z, Liu W (2003) Synthesis, structure and antibacterial activities of novel ferrocenyl-containing 1-phenyl-3-ferrocenyl-4-triazolyl-5-aryl-dihydropyrazole derivatives. J Organomet Chem 674:1–9

Farghaly AM, Soliman FSG, El Semary MMA, Rostom SAF (2001) Polysubstituted pyrazoles, part 4: synthesis, antimicrobial and anti-inflammatory activity of some pyrazoles. Pharmazie 56:28–32

Fonteh P, Keter FK, Meyer D, Guzei IA, Darkwa J (2009) Tetrachloro-bis(3, 5-dimethylpyrazolylmethane)gold(III) chloride: an HIV-1 reverse transcriptase and protease inhibitor. J Inorg Biochem 103:190–194

Gama S, Mendes F, Marques F, Santos IC, Carvalho MF, Correia I, Pessoa JC, Santos I, Paulo A (2011) Copper(II) complexes with tridentate pyrazole-based ligands: synthesis, characterization, DNA cleavage activity and cytotoxicity. J Inorg Biochem 105:637–644

Gamage SA, Spicer JA, Rewcastle GW, Milton J, Sohal S, Dangerfield W, Mistry P, Vicker N, Charlton PA, Denny WA (2002) Structure–activity relationships for pyrido-, imidazo-, pyrazolo-, pyrazino-, and pyrrolophenazinecarboxamides as topoisomerase-targeted anticancer agents. J Med Chem 45:740–743

Garg HG, Singhal A, Mathur JML (1973) Synthesis and biological activity of 1,5-diphenyl-4-arylazopyrazoles and 5,5-dimethylcyclohexane-1,2,3-trione-bishydrazones. J Pharm Sci 62:494–496

Genin MJ, Allwine DA, Anderson DJ, Barbachyn MR, Emmert DE, Garmon SA, Graber DR, Grega KC, Hester JB, Hutchinson DK, Morris J, Reischer RJ, Ford CW, Zurenko GE, Hamel JC, Schaadt RD, Stapert D, Yagi BH (2000a) Substituent effects on the antibacterial activity of nitrogen–carbon-linked (azolylphenyl)oxazolidinones with expanded activity against the fastidious gram-negative organisms haemophilus influenzae and moraxella catarrhalis. J Med Chem 43:953–970

Genin MJ, Biles C, Keiser BJ, Poppe SM, Swaney SM, Tarpley WG, Yagi Y, Romero DL (2000b) Novel 1,5-Diphenylpyrazole nonnucleoside HIV-1 reverse transcriptase inhibitors with enhanced activity versus the delavirdine-resistant P236L mutant: lead identification and SAR of 3- and 4-substituted derivatives. J Med Chem 43:1034–1040

Graham J, Muhsin M, Kirkpatrick P (2004) Oxaliplatin. Nat Rev Drug Discov 3:11–12

Haque TS, Tadesse S, Marcinkeviciene J, Rogers MJ, Sizemore C, Kopcho LM, Amsler K, Ecret LD, Zhan DL, Hobbs F, Slee A, Trainor GL, Stern AM, Copeland RA, Combs AP (2002) Parallel synthesis of potent, pyrazole-based inhibitors of helicobacter pylori dihydroorotate dehydrogenase. J Med Chem 45:4669–4678

Harrap KR (1985) Preclinical studies identifying carboplatin as a viable cisplatin alternative. Cancer Treat Rev 12:21–23

Hirschmann R, Buchschacher P, Steinberg NG, Fried JH, Ellis R, Kent GJ, Tishler M (1964) Synthesis and structure of steroidal Pregn-4-eno- and 5α-Pregnano [3,2-c]pyrazoles. A novel class of potent anti-inflammatory steroids. J Am Chem Soc 86:1520–1527

Johansson A, Poliakov A, Åkerblom E, Lindeberg G, Winiwarter S, Samuelsson B, Danielson UH, Hallberg A (2002) Tetrapeptides as potent protease inhibitors of hepatitis C virus full-length NS3 (protease–helicase/NTPase). Bioorg Med Chem 10:3915–3922

Jungheim LN (1989) Bicyclic pyrazolidinone antibacterial agents. Synthesis of side chain analogues of carbapenems PS-5 and thienamycin. Tetrahedron Lett 30:1889–1892

Kaymakcıoglu BK, Rollas S (2002) Synthesis, characterization and evaluation of antituberculosis activity of some hydrazones. Il Farmaco 57:595–599

Kees KL, Fitzgerald JJ Jr, Steiner KE, Mattes JF, Mihan B, Tosi T, Mondoro D, McCaleb ML (1996) New potent antihyperglycemic agents in db/db mice: synthesis and structure–activity relationship studies of (4-substituted benzyl)(trifluoromethyl)pyrazoles and -pyrazolones. J Med Chem 39: 3920–3928

Kelland LR, Sharp SY, O'Neill CF, Raynaud FI, Beale PJ, Judson IR (1999) Mini-review: discovery and development of platinum complexes designed to circumvent cisplatin resistance. J Inorg Biochem 77:111–115

Keter FK, Kanyanda S, Darkwa J, Rees DJG, Meyer M (2008) In vitro evaluation of dichloro-bis(pyrazole)palladium(II) and dichloro-bis(pyrazole)platinum(II) complexes as anticancer agents. Cancer Chemother Pharmacol 63:127–138

Keter FK, Nell MJ, Omondi B, Guzei IA, Darkwa J (2009a) Anticancer activities of bis(pyrazol-1-ylthiocarbonyl)disulfides against HeLa cells. J Chem Res 5:322–325

Keter FK, Ojwach SO, Oyetunji OA, Guzei IA, Darkwa J (2009b) Bis(pyrazolyl) palladium(II), platinum(II) and gold(III) complexes: syntheses, molecular structures and substitution reactions with L-cysteine. Inorg Chim Acta 362:2595–2602

Kidani Y, Noji M, Tashiro T (1980) Antitumor activity of platinum(II) complexes of 1,2-diamino-cyclohexane isomers. Gann 71:637–643

Komeda S, Lutz M, Spek AL, Chikuma M, Reedijk J (2000) New antitumor-active azole-bridged dinuclear platinum(II) complexes: synthesis, characterization, crystal structures, and cytotoxic studies. Inorg Chem 39:4230–4236

Kratz F, Nuber B, Weiss J, Keppler BK (1992) Synthesis and characterization of potential antitumour and antiviral gallium(III) complexes of *N*-heterocycles. Polyhedron 11:487–498

Kucukguzel SG, Rollas S, Erdeniz H, Kivaz M, Ekinci AC, Vidin A (2000) Synthesis, characterization and pharmacological properties of some 4-arylhydrazono-2-pyrazoline-5-one derivatives obtained from heterocyclic amines. Eur J Med Chem 35:761–771

Kulkarni NV, Revankar VK (2011) Synthesis, antimicrobial screening, and DNA-binding/cleavage of new pyrazole-based binuclear $Co^{II}$, $Ni^{II}$, $Cu^{II}$, and $Zn^{II}$ complexes. J Coord Chem 64:725–741

La Colla P, Manfredini S, Simoni D, Baraldi PG, Pani A (1996) Pyrazole-related derivatives endowed with antitumor and antiviral activities, procedures for their preparation, pharmaceutical formulations containing them. Pat. No. WO/1996/040704

Li TK, Theorell H (1969) Human liver alcohol dehydrogenase: inhibition by pyrazole and pyrazole analogs. Acta Chem Scand 23:892–902

Li H, Nukui S, Scales SA, Teng' M, Yin C (2010). Novel 3-aminopyrrolo[3,4-C]pyrazole-5(1H, 4H, 6H) carbaldehyde derivatives. Pat No. 20100130501

Li G, Fathi R, Yang Z, Liao Y, Zhu Q, Lam A, Sandrasagra A, Nawoschik K, Cho H-J, Cao J, Ruoqiu W, Wobbe CR, Liu Y (2011) 4-Ethnyl pyrazole derivative compounds and methods for treatment of HCV. Pat. No. US 7923004

Mahmud K, Khan MA, Iqbal MZ (2001) Antibacterial property of some transition metal complexes of pyrazole derivatives. Pak J Biol Sci 4:1000–1001

Manfredini S, Bazzanini R, Baraldi PG, Guarneri M, Simoni D, Marongiu ME, Pani A, La Colla P, Tramontano E (1992) Pyrazole-related nucleosides. Synthesis and antiviral/antitumor activity of some substituted pyrazole and pyrazolo[4,3-d]-1,2,3-triazin-4-one nucleosides. J Med Chem 35: 917–924

Manikannan R, Venkatesan R, Muthusubramanian S, Yogeeswari P, Sriram D (2010) Pyrazole derivatives from azines of substituted phenacyl aryl/cyclohexyl sulfides and their antimycobacterial activity. Bioorg Med Chem Lett 20: 6920–6924

Menozzi G, Mosti L, Fossa P, Mattioli F, Ghia M (1997) ω-Dialkylaminoalkyl ethers of phenyl-(5-substituted 1-phenyl-1H-pyrazol-4-yl)methanols with analgesic and anti-inflammatory activity. J Heterocycl Chem 34:963–968

Mosoarca EM, Pantenburg I, Tudose R, Meyer G, Popa NC, Han A, Alexandrova R, Kalfin R, Linert W, Costisor O (2011) Synthesis, structure and cytotoxic activity of mixed-valent Cu(I)/Cu(II) salt containing a pyrazolone derivative as ligand. Inorg Chim Acta. doi:10.1016/j.ica.2011.02.035

Moukha-chafiq O, Taha ML, Lazrek HB, Vasseur J–J, Pannecouque C, Witvrouw M, De Clercq E (2002) Synthesis and biological activity of some 4-substituted 1-[1-(2,3-dihydroxy-1-propoxy)methyl-1,2,3-triazol-(4&5)-ylmethyl]-1H-pyrazolo[3,4-d]pyrimidines. Farmaco 57:27–32

Narlawar R, Baumann K, Schubenel R, Schmidt B (2007) Curcumin derivatives inhibit or modulate beta-amyloid precursor protein metabolism. Neurodegener Dis 4:88–93

Narlawar R, Pickhardt M, Leuchtenberger S, Baumann K, Krause S, Dyrks T, Weggen S, Mandelkow E, Schmidt B (2008) Curcumin-derived pyrazoles Swiss army knives or blunt Alzheimer's disease? ChemMedChem 3:165–172

Negm NA, Said MM, Morsy SMI (2010) Pyrazole derived cationic surfactants and their tin and copper complexes: synthesis, surface activity, antibacterial and antifungal efficacy. J Surfactants Deterg 13:521–528

Nomiya K, Noguchi R, Ohsawa K, Tsuda K, Oda M (2000) Synthesis, crystal structure and antimicrobial activities of two isomeric gold(I) complexes with nitrogen-containing heterocycle and triphenylphosphine ligands, [Au(L)$(PPh_3)$] (HL = pyrazole and imidazole). J Inorg Biochem 78:363–370

Onoa GB, Moreno V, Font-Bardia M, Solans X, Pérez JM, Alonso C (1999) Structural and cytotoxic study of new Pt(II) and Pd(II) complexes with the bi-heterocyclic ligand mepirizole. J Inorg Biochem 75:205–212

Ouyang G, Cai X-J, Chen Z, Song B-A, Bhadury PS, Yang S, Jin L-H, Xue W, Hu D-Y, Zeng S (2008) Synthesis and antiviral activities of pyrazole derivatives containing an oxime moiety. J Agric Food Chem 56:10160–10167

Pancic F, Steinberg BA, Diana GD, Carabateas PM, Gorman WG, Came PE (1981) Antiviral activity of Win 41258-3, a pyrazole compound, against herpes simplex virus in mouse genital infection and in guinea pig skin infection. Antimicrob Agents Chemother 19:470–476

Panda J, Srinivas SV, Rao ME (2002) Synthesis and antimicrobial activity of some pyrazoline derivatives of 4(3H)-quinazolinones. J Indian Chem Soc 79:770–776

Park H-J, Lee K, Park S-J, Ahn B, Lee J-C, Cho HY, Lee K-I (2005) Identification of antitumor activity of pyrazole oxime ethers. Bioorg Med Chem Lett 15:3307–3312

Pereira EF, Aracava Y, Aronstam RS, Barreiro EJ, Albuquerque EXJ (1992) Pyrazole, an alcohol dehydrogenase inhibitor, has dual effects on *N*-methyl-D-aspartate receptors of hippocampal pyramidal cells: agonist and noncompetitive antagonist. Pharmacol Exp Ther 261:331–340

Pettinari C, Caruso F, Zaffaroni N, Villa R, Marchetti F, Pettinari R, Phillips C, Tanski J, Rossi M (2006) Synthesis, spectroscopy (IR, multinuclear NMR, ESI-MS), diffraction, density functional study and in vitro antiproliferative activity of pyrazole-beta-diketone dihalotin(IV) compounds on 5 melanoma cell lines. J Inorg Biochem 100: 58–69

Pinto DCGA, Silva AMS, Cavaleiro JAS, Foces-Foces C, Llamas-Saiz AL, Jagerovic N, Elguero J (1999) Synthesis and molecular structure of 3-(2-benzyloxy-6-hydroxyphenyl)-5-styrylpyrazoles. Reaction of 2-styrylchromones and hydrazine hydrate. Tetrahedron 55:10187–10200

Radi S, Salhi S, Radi A (2010) Synthesis and preliminary biological activity of some new pyrazole derivatives as acyclonucleoside analogues. Lett Drug Des Discov 7:27–30

Rathelot P, Azas N, El-Kashef H, Delmas F, Di Giorgio C, Timon-David P, Maldonado J, Vanelle P (2002) 1,3-Diphenylpyrazoles: synthesis and antiparasitic activities of azomethine derivatives. Eur J Med Chem 37:671–679

Rosenberg B, van Camp L, Krigas T (1965) Inhibition of cell division in *Escherichia coli* by electrolysis products from a platinum electrode. Nature 205:698–699

Rosenberg B, van Camp L, Trosko JE, Mansour VH (1969) Platinum compounds: a new class of potent antitumour agents. Nature (London) 222:385–386

Rostom SAF, Shalaby MA, El-Demellawy MA (2003) Polysubstituted pyrazoles, part 5. Synthesis of new 1-(4-chlorophenyl)-4-hydroxy-1H-pyrazole-3-carboxylic acid hydrazide analogs and some derived ring systems. A novel class of potential antitumor and anti-HCV agents. Eur J Med Chem 38:959–974

Russell AD, Hugo WB (1994) Antimicrobial activity and action of silver. Prog Med Chem 31:351–370

Sakai K, Tomista Y, Ue T, Goshima K, Ohminato M, Tsubomura T, Matsumoto K, Ohmura K, Kawakami K (2000) Syntheses, antitumor activity, and molecular mechanics studies of cis-PtCl2(pzH)2 (pzH=pyrazole) and related complexes. Crystal structure of a novel Magnus-type double-salt [Pt(pzH)4][PtCl4][cis-PtCl2(pzH)2]2 involving two perpendicularly aligned 1D chains. Inorg Chim Acta 297:64–71

Sau DK, Butcher RJ, Chaudhuri S, Saha N (2003) Spectroscopic, structural and antibacterial properties of copper(II) complexes with bio-relevant 5-methyl-3-formylpyrazole N(4)-benzyl-N(4)-methylthiosemicarbazone. Mol Cell Biochem 253:21–29

Segapelo TV, Guzei IA, Spencer LC, Van Zyl WE, Darkwa J (2009) (Pyrazolylmethyl)pyridine platinum(II) and gold (III) complexes: synthesis, structures and evaluation as anticancer agents. Inorg Chim Acta 362:3314–3324

Sharma KV, Sharma V, Tripathi UN (2009) Synthesis, spectroscopic, antibacterial and antifungal studies of nickel(II)5 (2′-hydroxyphenyl)-3-(4-X-phenyl)pyrazolinates and their addition complexes with N and P donor ligands. J Coord Chem 62:676–690

Shen D-M, Shu M, Mills SG, Chapman KT, Malkowitz L, Springer MS, Gould SL, DeMartino JA, Siciliano SJ, Kwei GY, Carella A, Carver G, Holmes K, Schleif WA, Danzeisen R, Hazuda D, Kessler J, Lineberger J, Miller MD, Emini EA (2004a) Antagonists of human CCR5 receptor containing 4-(pyrazolyl)piperidine side chains. Part 1: discovery and SAR study of 4-pyrazolylpiperidine side chains. Bioorg Med Chem Lett 14:935–939

Shen D-M, Shu M, Willoughby CA, Shah S, Lynch CL, Hale JJ, Mills SG, Chapman KT, Malkowitz L, Springer, Gould SL, DeMartino JA, Siciliano SJ, Lyons K, Pivnichny JV, Kwei GY, Carella A, Carver G, Holmes K, Schleif WA, Danzeisen R, Hazuda D, Kessler J, Lineberger J, Miller MD, Emini EA (2004b) Antagonists of human CCR5 receptor containing 4-(pyrazolyl)piperidine side chains. Part 2: Discovery of potent, selective, and orally bioavailable compounds. Bioorg Med Chem Lett 14:941–945

Shih SR, Chu TY, Reddy GR, Tseng SN, Chen HL, Tang WF, Wu MS, Yeh JY, Chao YS, Hsu JT, Hsieh HP, Horng JT (2010) Pyrazole compound BPR1P0034 with potent and selective anti-influenza virus activity. J Biomed Sci 23: 13–17

Shipps Jr GW, Curran PJ, Annis DA, Nash HM, Cooper AB, Zhu HY, Wang J J-S, Desai JA, Girijavallabhan V (2006a) Substituted5-carboxyamide pyrazoles and [1,2,4] triazoles as antiviral agents. Pat. No. WO/2006/050034

Shipps Jr GW, Wang T, Rosner KE, Curran PJ, Cooper AB, Girijavallabhan VM (2006b) Substituted 5-oxo pyrazoles and [1,2,4] triazoles as antiviral agents. Pat. No. US711 5749

Stauffer SR, Coletta CJ, Tedesco R, Nishiguchi G, Carlson K, Sun J, Katzenellenbogen BS, Katzenellenbogen JA (2000) Pyrazole ligands: structure–affinity/activity relationships and estrogen receptor-α-selective agonists. J Med Chem 43:4934–4947

Stauffer SR, Huang YR, Aron ZD, Coletta CJ, Sun J, Katzenellenbogen BS, Katzenellenbogen JA (2001) Triarylpyrazoles with basic side chains: development of pyrazole-based estrogen receptor antagonists. Bioorg Med Chem 9: 151–161

Storer R, Ashton CJ, Baxter AD, Hann MM, Marr CLP, Mason AM, Mo C-L, Myers PL, Noble SA, Penn CR, Weir NG, Woods JM, Coe PL (1999) The synthesis and antiviral

activity of 4-fluoro-1-β-d-ribofuranosyl-1H-pyrazole-3-carboxamide. Nucleotides 18:203–216

Sweeney ZK, Harris SF, Arora N, Javanbakht H, Li Y, Fretland J, Davidson JP, Billedeau JR, Gleason SK, Hirschfeld D, Kennedy-Smith JJ, Mirzadegan T, Roetz R, Smith M, Sperry S, Suh JM, Wu J, Tsing S, Villasenor AG, Paul A, Su G, Heilek G, Hang JQ, Zhou AS, Jernelius JA, Zhang F-J, Klumpp K (2008) Design of annulated pyrazoles as inhibitors of HIV-1 reverse transcriptase. J Med Chem 51:7449–7458

Takabatake E, Kodama R, Tanaka Y, Dohmori R, Tachizawa H, Naito T (1970) The metabolic fate of 1-(4-methoxy-6-methyl-2-pyrimidinyl)-3-methyl-5-methoxypyrazole (mepirizole, DA-398) in rats and rabbits. Chem Pharm Bull 18:1900–1907

Tanitame A, Oyamada Y, Ofuji K, Fujimoto M, Iwai N, Hiyama Y, Suzuki K, Ito H, Terauchi H, Kawasaki M, Nagai K, Wachi M, Yamagishi J (2004) Synthesis and antibacterial activity of a novel series of potent DNA gyrase inhibitors. Pyrazole derivatives. J Med Chem 47:3693–3699

Tharmaraj P, Kodimunthiri D, Sheela CD, Priya CS (2009) Synthesis, spectral studies and antibacterial activity of Cu(II), Co(II) and Ni(II) complexes of 1-(2-hydroxyphenyl)-3-phenyl-2-propan-1-one, N2-[(3,5-diemthyl-1H-pyrazol-1-yl)methyl]hydrazone. J Serb Chem Soc 74: 927–938

Theorell H, Yonetani T (1963) Liver alcohol dehydrogenase-DPN-pyrazole complex: a model of a ternary intermediate in the enzyme reaction. Biochem Z 338:537–553

Theorell H, Yonetani T, Sjoberg B (1969) On the effects of some heterocyclic compounds on the enzymatic activity of liver alcohol dehydrogenase. Acta Chem Scand 23:255–260

Tobe ML, Khokhar AR (1977) Structure, activity, reactivity and solubility relationships of platinum diamine complexes. J Clin Hematol Oncol 7:114–137

Vitolo MJ, Marquez VE, Hurtado I (1978) trans-2,3b, 4,5,7,8b,9,10-Octahydronaphtho[1,2-c:5,6-c']dipyrazole, a new orally active antiallergic compound. J Med Chem 21:692–694

Wheate NJ, Collins JG (2003) Multi-nuclear platinum complexes as anti-cancer drugs. Coord Chem Rev 241:133–145

Wheate NJ, Cullinane C, Webster LK, Collins JG (2001) Synthesis, cytotoxicity, cell uptake and DNA interstrand cross-linking of 4,4-dipyrazolylmethane-linked multinuclear platinum anti-cancer complexes. Anticancer Drug Des 16: 91–98

Wu L, Song B, Bhadury PS, Yang S, Hu D, Jin L (2011) Synthesis and antiviral activity of novel pyrazole amides containing α-aminophosphonate moiety. J Heterocycl Chem 48:389–396

Zhang Y, Zhang L, Liu L, Guo J, Wu D, Xu G, Wang X, Jia D (2010) Anticancer activity, structure, and theoretical calculation of *N*-(1-phenyl-3-methyl-4-propyl-pyrazolone-5)-salicylidene hydrazone and its copper(II) complex. Inorg Chim Acta 363:289–293

Zhou H-B, Sheng S, Compton DR, Kim Y, Joachimiak A, Sharma S, Carlson KE, Katzenellenbogen BS, Nettles KW, Greene GL, Katzenellenbogen JA (2007) Structure-guided optimization of estrogen receptor binding affinity and antagonist potency of pyrazolopyrimidines with basic side chains. J Med Chem 50:399–403