RECENT TRENDS IN BIOCHEMISTRY

Synthesis, Antibacterial and Anti-Tumor Activity of Pyrazole Derivatives

Maria Marinescu; Christina-Marie Zalaru*

Department of Organic Chemistry, Biochemistry and Catalysis, University of Bucharest, Bucharest, 90-92 Panduri Road, Romania.

Corresponding Author: Christina-Marie Zalaru

Department of Organic Chemistry, Biochemistry and Catalysis, University of Bucharest, Bucharest, 90-92 Panduri Road, Romania.

Email: chmzalaru@gmail.com

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Abstract

The pyrazolic nucleus has a multitude of activities such as analgesic, antiarrhythmic, local anesthetic, antimicrobial, anticonvulsivant, anti-tumor, antidiabetic, antipyretic, antiviral, antimalarial, and so forth. The literature is extremely abundant in the study of pyrazoles, their synthesis and medicinal applications.

Synthesis strategies on the pyrazolic nucleus have expanded in recent times, so that hybrid pyrazolic nuclei with other heterocyclic nuclei have been obtained.

We propose in this chapter to present strategies of synthesis of the pyrazolic nucleus, with antibacterial and anti-tumor properties. The relationship structure-activity is described.

Introduction

The pyrazolic nucleus possesses a variety of activities such as antipyretic, antimicrobial, analgesic, anti-inflammatory, anti-tumor, antiviral, antidiabetic, anti-hypertensive, anesthetic local, antimicrobial, reno-protective, antioxidant and Monoamine oxidase B (MAO-B) inhibitory activities [1-20]. The pyrazolic nucleus is found in a suite of drugs, as shown in

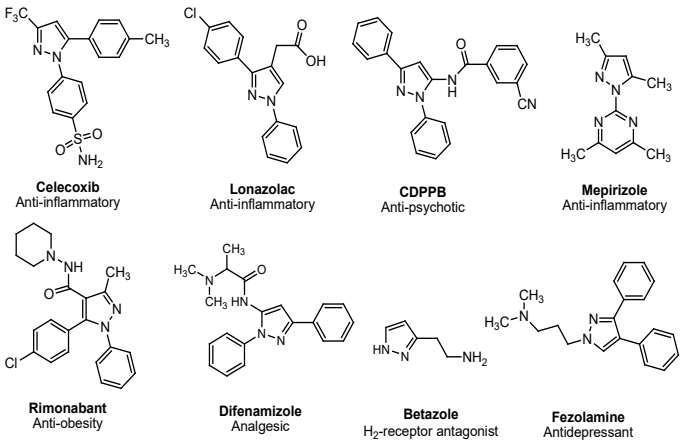

Figure 1: Marketed pyrazole-containing drugs.

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1. Characteristic properties as pyrazoles

Pyrazole belongs to the fundamental heterocyclic system with aromatic character, from the azole class consisting of three carbon atoms and two nitrogen atoms of a pyrrolic type and pyridinic type, in positions 1 and respective 2 (Figure 2) [21,22]. Thus pyrazole itself boils at 187-188°C and melts at 70°C. It forms intermolecular hydrogen bonds. Pyrazole and the lower homologes dissolve readily in the majority of organic solvents and in water. Pyrazole has character amphoter though more notably basic than acidic [21]. Thus it forms easily hydrolyzed salts with strong acids, whereas it can give sodium and potassium salts. These too are easily hydrolyzed by water (Figure 3) [21,22].

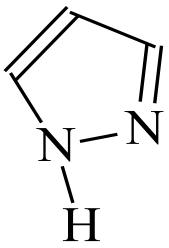


Figure 2: The chemical structure of pyrazole.

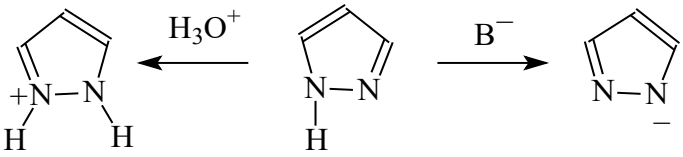


Figure 3: Ion structure of the pyrazolic nucleus.

Pyrazole exists in two identical and inseparable tautomere forms due to rapid interconversion (Figure 4) [21,22].

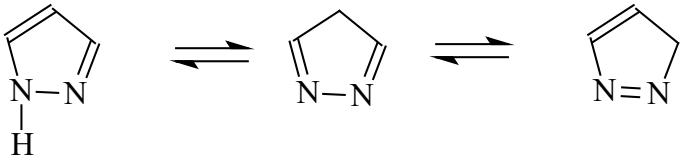


Figure 4: Tautomers of unsubstituted pyrazole.

It is more correct to explain the tautomerism of pyrazoles by saying that at protonation forms the same cation, and with the bases form the same anion, from either uncharged form of pyrazoles (Figure 5) [22].

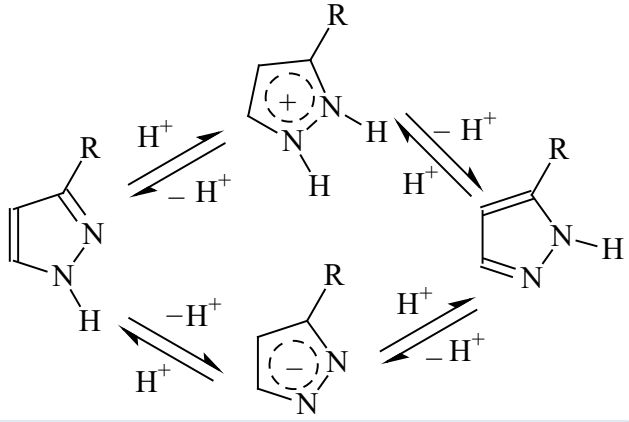


Figure 5: Tautomers of unsubstituted pyrazole.

The pyrazolic nucleus forms cyclic dimers and trimers through intermolecular hydrogen associations (Figure 6).

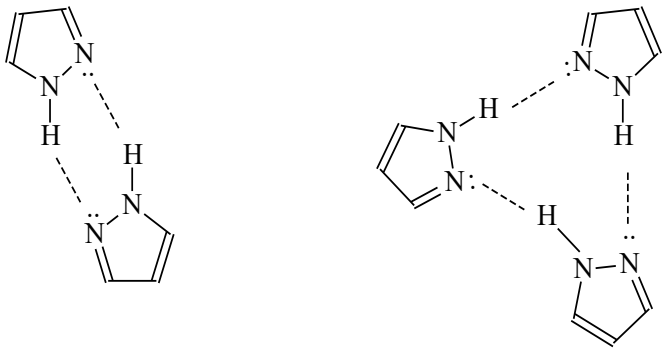


Figure 6: The association of pyrazoles.

I. Pyrazoles as antibacterials

The resistance of microbial strains to classic drugs synthesized in recent years is one of the central medical problems. Therefore, one of the research directions of chemists is the synthesis of new compounds with antimicrobial properties. Pyrazole compounds are important components in antibacterial drug discovery [23]. Akbas et *al.* reported the synthesis of a new 1*H*-pyrazole-3-carboxylic derivatives (Figure 7). All pyrazoles were evaluated for the antibacterial activities against *Bacillus cereus, Staphylococcus aureus, Escherichia coli* and *Pseudomonas putida.* Compound 1 exhibited the best antibacterial activity against both Gram-positive and Gram-negative bacteria (Figure 7) [24].

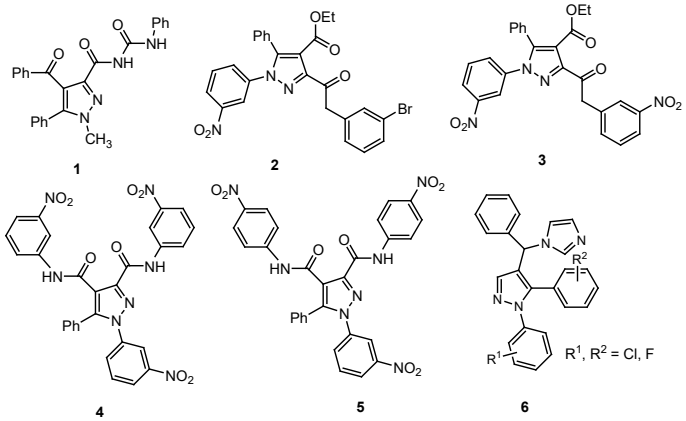


Figure 7: Pyrazoles with antimicrobial activity.

A series of pyrazole-3-carboxylic acid and pyrazole-3,4-dicarboxylic acid derivatives were synthesized and assessed for their antimicrobial activities against five bacterial and five fungal pathogens. The molecules 2, 3, 4 and 5 showed good inhibitory effects on *Candida tropicalis*, *Candida parapsilosis* and *Candida glabrata* strains [25]. A series of bifonazole heteroanalogues, 4-[1*H*-imidazol-1-yl(phenyl)]-1,5-diphenyl-1*H*-pyrazole 6, was synthesized and evaluated for their *in vitro* antimicrobial activities against selected pathogens. Some dichloro- and trichloropyrazole derivatives showed outstanding antimicrobial effects [26]. A series of 3-substituted-5-(benzofuran-2-yl)-pyrazoles posses remarkable antibacterial activities against *Bacillus subtilis*. 5(Benzofuran-2-yl)-1*H*-pyrazole-3-carbohydrazide 7 has even larger inhibition zones than Amoxicillin (Figure 8) [27]. The synthesis 5-amido-1-(2,4-dinitrophenyl)-1*H*-4-pyrazole carbonitriles 8 was reported by Rahimizadeh et *al*. Their *in vitro* antimicrobial activity were showed against methicillin resistant and methicillin susceptible *Staphylococcus aureus*. All pyrazoles

showed good activities, with MIC values of 25.1 and 91.0 µM, respectively, against both methicillin susceptible and methicillin resistant *S. aureus* [28].

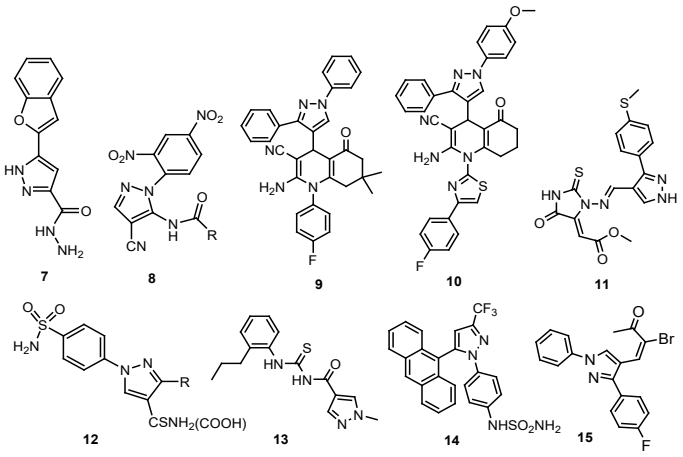


Figure 8: Pyrazoles with antimicrobial activity [36-43].

Thumar and Patel reported that 2-amino-4-(1,3-diphenyl-1H-pyrazol-4-yl)-1-(4-fluoro phenyl) 7,7-dimethyl-5-oxo -1,4,5,6,7,8 -hexahydroquinoline-3-carbonitrile 9 and 2-amino-1-(4--(4-fluorophenyl)thiazol-2-yl)-4-(3-(4-methoxyphenyl)-1-phenyl-1H-pyrazol-4-yl)-5-oxo-1,4,5,6, 7,8-hexahydroquinoline -3-carbonitrile 10 displayed comparable activity to that of ampicillin against *Streptococcus pneumoniae* (MIC=100 µg/mL) [29]. Vijesh et *al.* synthesized new substituted pyrazoles containing imidazole moiety. Compound 11 exhibited antimicrobial activity compared to streptomycin against *P. aeruginosa* at the concentrations of 1 and 0.5 mg/mL [30]. Several 4-functionalized pyrazoles 12 were synthesized and their *in vitro* antibacterial activity was evaluated against four pathogens: *Escherichia coli* and *Pseudomonas aeruginosa* (Gram-negative), *Staphylococcus aureus* and *Bacillus subtilis* (Gram-positive). Some of these pyrazoles posess middle activity against Gram positive bacteria [31]. Nitulescu et *al.* reported the synthesis of N-(1-methyl-1*H*-pyrazole-4-carbonyl)-thiourea derivatives. They found that compound 13 had an important action on the bacterial soluble enzymatic factors expression and inhibited the caseinase production in *E. coli* [32]. N-[4-(5-anthracen-9-yl-3-trifluoromethyl-pyrazol-1-yl)phenyl]-aminosulfonamide 14 showed good antibacterial activity and time-dependent death of *S. aureus* [33]. The group of Pundeer reported the synthesis of (Z)-3-bromo-4-(3-(4-fluorophenyl)-1-phenyl-1*H*-pyrazol-4-yl) but-3-en-2-one 15 and its good antibacterial activity with MIC value of 32 µg/mL [34] (Figure 8).

Desai et *al.* reported the synthesis of 6-amino-1-((1,3-diphenyl-1*H*-pyrazole-4-yl)methylene amino)-4-(aryl)-2oxo-1,2-dihydropyridine-3,5-dicarbonitriles. At non-cytotoxic concentrations, compounds 16 demonstrated the maximum inhibition against nearly all bacteria tested (Figure 9) [35]. 2,5-Dichlorothiophene-substituted pyrazole compound 17, exhibited the best antimicrobial activity against *S. aureus* compared to Ceftriaxone and resembling activity against *B. subtilis* and *P. aeruginosa* consiering the same standard drug [36]. Ragavan *et al*. reported the synthesis of sulfisoxazole-pyrazole dcompounds [37]. 5-amino-1*H*-pyrazole-amide 18 showed the best antimicrobial activities than the other sulfisoxasole compounds against most bacteria tested.

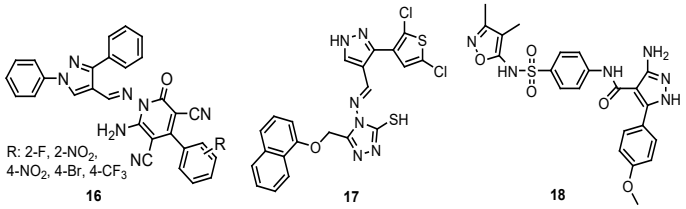


Figure 9: Pyrazoles with antimicrobial activity.

The synthesis and the antimicrobial activity of new quinolinyl pyrazole chalcones was reported by Prasath group (Figure 9). The best antimicrobial activity against all tested strains was found for compound 19 (Figure 10) [38]. Kendre et *al*. reported the synthesis and the antimicrobial activity of a pyrazole compounds repoted to ampicillin and norcadine as standard drugs. The best antimicrobial activity was found for compounds 20 and 21 [39].

Sayed group synthesized new pyrazole compounds and evaluated their antimicrobial activity. The best antimicrobial activity was found for compound 22 against the tested strains [40]. The synthesis of new antimicrobial pyrazoles was reported by Al-Ghamdi et *al*. Compound 23 was found to possess moderate activity against *Aspergillus fumigatus* [41]. Barakat group synthesized pyrazole-dimedone compounds using an one-pot multicomponent reaction and evaluated their antimicrobial activiy. All synthesized pyrazoles were tested for their antifungal and antibacterial activities against *C. albicans* ATCC 2091, *S. aureus* ATCC 29213, *E. faecalis* ATCC29212 and *B. subtilis* ATCC 10400. The best antimicrobial activity against S*. aureus* with MIC value of 16 µg/L was found for compounds 24 and 25 [42]. Cetin et *al*. reported the synthesis of 4-acyl-pyrazole-3-carboxylic acids 26-28. Their *in vitro* antibacterial activity against gram-positive (*B. subtilis*, *S. aureus*) and gram-negative (*K. pneumoniae, P. aeruginosa*, *E. coli*) bacteria was determined by diffusion method (Figure 10).

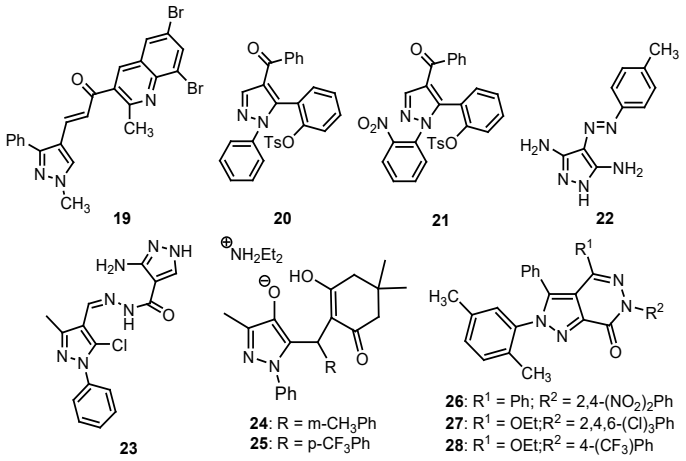


Figure 10: Pyrazoles with antimicrobial activity.

Pyrazole derivatives 26-28 exhibited higher activities than reference drugs against the representative bacteria [43]. Nalawade et *al.* reported the synthesis of a series of 1-substituted benzyl-4-[1-phenyl-3-(4-methyl-2-aryl-1,3-thiazol-5-yl)-1*H*-pyrazol-4-yl]-1*H*-1,2,3-triazole derivatives by click reaction. The antimicrobial activity of the new synthesized compounds weas screened against *Escherichia coli* (NCIM 2574), *Proteus mirabilis* (NCIM 2388) (Gram negative) and *Staphylococcus albus* (NCIM 2178) (Gram positive) strains and *in vitro* antifungal activity against *Aspergillus niger* (ATCC 504), *Candida albicans* (NCIM 3100) and *Rhodotorula glutinis* (NCIM 3168).

A good antifungal activity against *A. niger* with MIC 31.5 µg/mL was found for 1,2,3-triazole-thiazolyl-pyrazolyl compounds 29-38 (Figure 11) [44,45]. Reddy et *al*. prepared new bis heterocycles-benzimidazolyl pyrazoles with antimicrobial activity. The nitro-aromatic derivative 39 having was found to possess the best antimicrobial activity against *Penicillium chrysogenum* and *Pseudomonas aeruginosa* [46]. Desai et *al*. synthesized new nitro pyrazole based thiazole derivatives. The *in vitro* antibacterial activity against *Streptococcus pyogenes*, *Staphylococcus aureus,* (Gram-positive), *Pseudomonas aeruginosa Escherichia coli,* (Gram-negative bacteria) and *Aspergillus niger, Aspergillus clavatus, Candida albicans* (Fungi) was reported. Compound 40 showed remarkable antibacterial and antifungal activity against all strains tested [47].

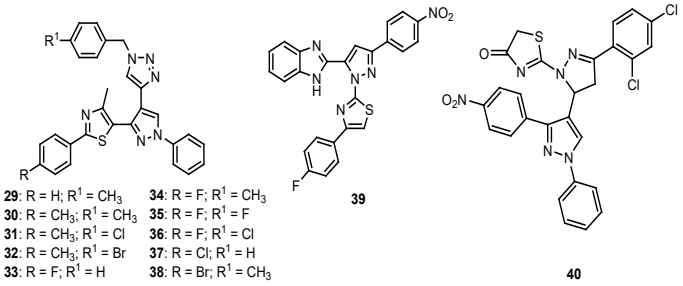
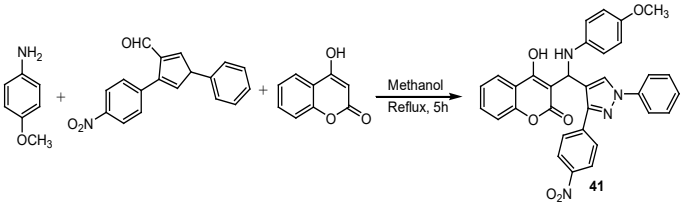


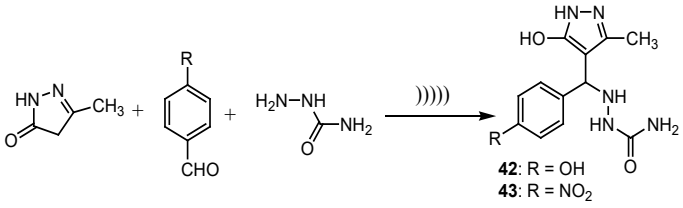
Figure 11: Pyrazoles with antimicrobial activity.

Kovvuri et *al.* synthesized a series a pyrazole-coumarin compounds by a multicomponent reaction between a pyrazole aldehyde, aniline and 4-hydroxycoumarin (Scheme 1).



Scheme 1: Synthesis of the pyrazole-coumarin derivative 41.

Compound 41 proved to have the best antibacterial and antifungal activity against all strains screened [48]. Kumar et *al.* synthesized new pyrazole compounds from 5(3)-hydroxy-3(5)-methyl-1*H*-pyrazoles, aldehyde and semicarbazide *via* ultrasound irradiation under aqueous medium and without catalysis condition, as you can see in Scheme 2. Compound 42 (MIC: 0.25 µg/mL) possess remarkable antibacterial activity against *Escherichia coli* (gram negative) and compound 43 (MIC: 0.25 µg/mL) was found to have the best antibacterial activity against *Streptococcus epidermidis* (gram positive) bacteria compared with standard Ciprofloxacin [49].



Scheme 2: Synthesis of the pyrazole compounds via Ultrasound irradiation

New N-((1,3-diphenyl-5-aryl-1H-pyrazol-4-yl)sulfonyl)thioph en ne-2-amides were synthesized starting to (E)-N-(arylethene sulfonyl)thiophene-2-carboxamides. The compounds 44 and 45 (Figure 12) showed potential antimicrobial activity against B. subtilis [50].

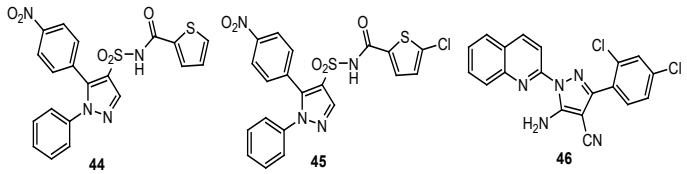


Figure 12: Pyrazoles with antimicrobial activity.

Shehry et *al.* found that the pyrazole compound 46 possess better antimicrobial ativity relative to the reference drugs as can be seen by their MIC values (0.12-0.98 µg/mL). Also, pyrazole 46 has been shown to be 4 times more effective than gentamicin in the antimicrobial activity of *S. flexneri* of MIC 0.12 mg/mL. Also, compound 46 has four times better antifungal activity than amphotericin B compared to *A. clavatus* (MIC 0.49 µg/mL) and *C. albicans* (MIC 0.12 µg/mL) [51].

New pyrazole-fused tricyclic diterpene derivatives was synthesized by Yu group. Compounds 47 and 48 exhibited highest antimicrobial activity against Newman strain of *S. aureus* with MIC value of 1 µg/mL. Pyrazoles 49 and 50 were reported to have the best antimicrobial activity against five multi-drug resistant *S. aureus* with MIC of 0.71-3.12 µg/mL (Figure 13) [52]. Wang et *al*. prepared multi-pyrazole derivatives and screened for their for antimicrobial activity. Compound 51 demonstrated maximum inhibitory effect of all reported derivatives against *Bacillus subtilis* [53]. In another series of pyrazole-oxadiazoles compounds developed by Malladi et *al*. Compound 52 was reported to exhibit excellent potency against *P. Aeruginosa, E. coli* and *S. aureus* [54].

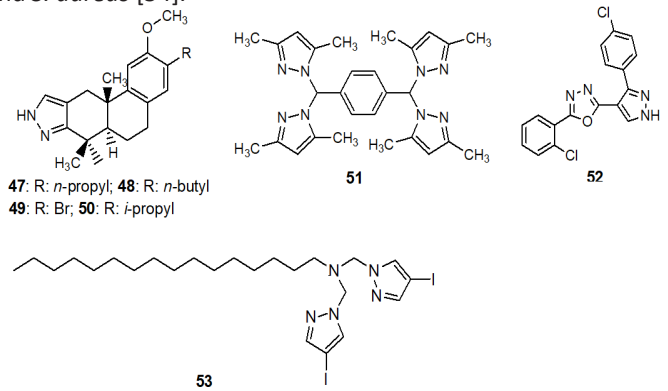
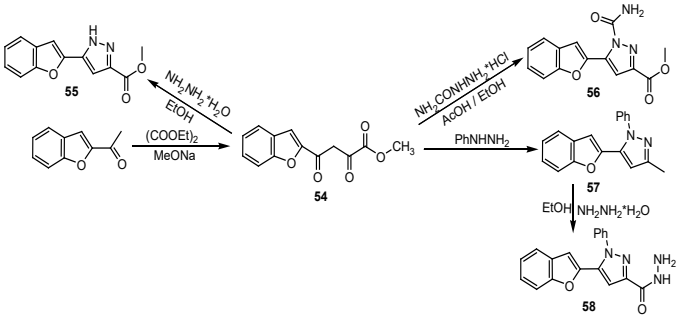


Figure 13: Pyrazoles with antimicrobial activity.

Zalaru el *al.* synthesized some alkylaminopyrazole derivatives and evaluated the *in vitro* antimicrobial activity against fungal and bacterial strains using clotrimazole and erythromycin as standards. The halogenated compound 53 with special pharmacophore structure possess the best antimicrobial activity against *Bacillus subtilis* (MIC=0.007 µgmL^{-1}) reported to erythromycin [17].

Siddiqui et *al*. synthesized new pyrazole-3-carboxylate compounds (55–58) from methyl 4-(benzofuran-2-yl)-2,4-dioxobutanoate 54 (Scheme 3). All pyrazoles possess antifungal and antibacterial propertis against *Bacillus subtilis* and *Staphylococcus aureus* (Gram-positive), *Escherichia coli* and *Pseudomonas aeruginosa* (Gram-negative) bacteria and one fungus (*Aspergillus niger*) [55].



Scheme 3: Synthesis of pyrazoles 55-58.

Compound 55 possess the best antifungal and antibacterial activity of all. Abdel-Wahab et *al.* reported the synthesis of new pyrazolyltriazole and dihydropyrazolylthiazole compounds. The products 59-60 displayed good antibacterial and antifungal activities against different types of bacteria and fungi [56] (Figure 14).

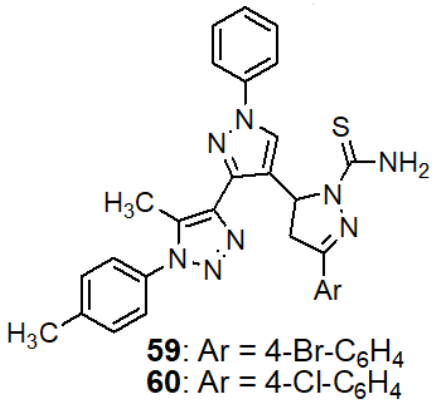


Figure 14: Pyrazoles with antimicrobial activity.

Harikrishna et *al* synthesized novel 1′-(4-chlorophenyl)-5-(substituted aryl)-3′-(substituted aryl)-3,4-dihydro-2*H*,1′*H*-[3,4′] bipyrazolyl derivatives and reported their antitubercular and antimicrobial activity. The best antimicrobial activities were reported for compounds 61 with MIC of 1.56 µg ml^{-1} and for 62 with MIC of 6.25 µg ml^{-1} as comparing with streptomycin and pyrazinamide as standard drugs (Figure 15) [57]. Ziarani et *al.* synthesized 6-amino-5-cyanodihydropyrano [2,3-c] pyrazoles using a green, one-pot and efficient method by three component condensation of 3-methyl-1*H*-pyrazole-5(4*H*)-one, malononitrile and aromatic aldehydes under mild reaction condition using propylamine functionalized nanoporous silica (NPS) as a heterogeneous solid base catalyst (Scheme 4). Compound 63 showed the best antimicrobial activity against *Staphylococcus aureus* and *Bacillus subtilis* [58].

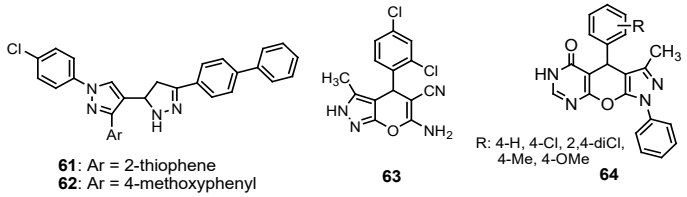
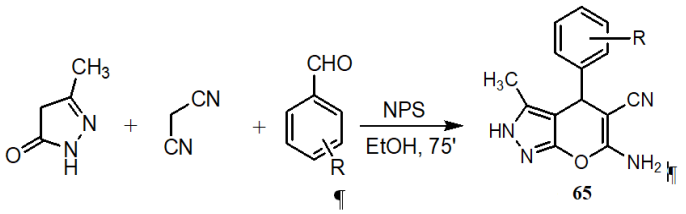


Figure 15: Pyrazoles with antimicrobial activity [64-66].

Hegde et *al.* synthesized new pyrimidine annulated dihydropyrano [2,3-c] pyrazole derivatives 64. The molecules possess good to moderate activity as antimicrobial agents considering ciprofloxacin as standard drug [59].



Scheme 4: Synthesis of pyrazoles 6-amino-5-cyanodihydropyrano [2,3-c] pyrazoles.

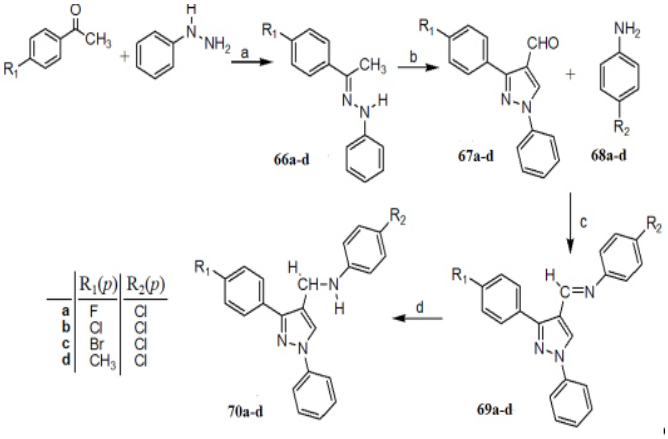
Pyrazoles as anti-tumors

Cancer is a scourge, being one of the causes of death and will become the most common disease [60,61]. About a third of reported deaths are due to smoking, the leading cause of lung cancer, while 20% of all diagnosed cancers are associated with obesity, physical inactivity, excessive alcohol consumption and / or poor nutrition. On the other hand, certain types of cancer are caused by infections such as Hepatitis C Virus (HCV), human papilloma virus (HPV), *Helicobacter pylori* (*H. pylori*). Hepatitis B (HBV), Human Immunodeficiency Virus (HIV). These cancers could be prevented by vaccination, treating the infection, or by behavioral changes [61].

Cancer cells divide uncontrollably by invading normal tissues and organs, then spreading throughout the body [61-63]. There is a major difference between a bening tumor, and a malignant tumor, the last one spreads throughout the body, through the lymphatic and circulatory systems. The main anomaly leading to the development of cancer is the continuous the proliferation of cancer cells as a result of loss of generalized growth control.

Although progress has been made in cancer therapy, from a therapeutic point of view it is followed by new derivatives pyrazolic compounds [61-63].

The synthetic route of the N-((1,3-diphenyl-1H-pyrazol-4-yl) methyl)aniline derivatives (70a-d) are outlined in Scheme 5. Compounds 66a-d were prepared by the condensation and cyclization of various substituted acetophenones with phenylhydrazine. The desired compounds 70a-d are obtained by direct reductive amination using $NaBH_4/I_2$. N-((1,3-diphenyl-1*H*-pyrazol-4-yl)methyl)aniline derivatives 69a-d were obtained from 1,3-diphenyl-1*H*-pyrazole-4-carbaldehyde 67a-d and substituted anilines 68a-d [64].

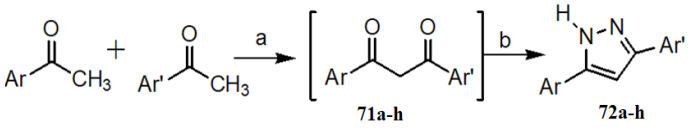


Scheme 5: (a). ethanol, 50–60 0C, 3h; (b). DMF, POCl3, 50–60 0C, 5h; (c). ethanol, 50–60 0C, 5h; d. tetrahydrofuran, NaBH4/I2, 50–60 0C, 12h.

Cellular lines like us H460 (large lung carcinoma cell), SW620 (colorectal adenocarcinoma cell), AGS (gastric carcinoma cell), OVCA (ovarian carcinoma cell), were used to highlight the growth inhibitory activity of 3,5-diaryl-1H-pyrazoli 71a-h–72a-h.

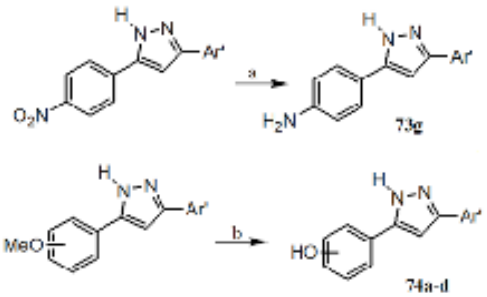
It is known the synthesis since 1893, by which 3,5-diaryl-1*H*-pyrazole are obtained by cyclization of 1,3-diketone with hydrazine [65].

The authors obtained 3,5-diaryl-1*H*-pyrazole 72a-h by the cyclization of 1,3-diketone with hydrazine. 1,3-Diketone 71a-h have been synthesized by the treatment of commercially available acetophenone and benzoyl chloride in the presence of strong base BuLi (Scheme 6) [66].



Scheme 6: (a). LiHMDS, toluene, reflux, 2h; (b). NH2NH2.HCl, EtOH, reflux, 16h.

Consequently, have been synthesized a series of 3,5-diaryl-1*H*-pyrazoles 73g, and 74a-d, by hydrogenation or demethylation reaction. (Scheme 7).

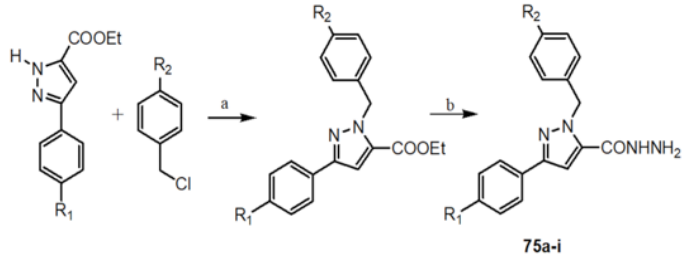


	Ar	Ar'
a	4-OMe	H
b	4-CF_3	2-OMe
c	2-OMe	3-OMe
d	3-OMe	4-OMe
e	2-OH	4-F
f	4-OH	4-Cl
g	4-NO_2	4-Br
h	4-NH_2	3,4-doOMe

Scheme 7: (a). Pd/C, H2, MeOH, rt, 16h; (b). BBr3, DCM.

A new series of substituted 1-arylmethyl-3-aryl-1*H*-pyrazole-5-carbohydrazide 75a-i were synthesized and evaluated the antitumor activity from Xia et al. All the compounds induced the cell apoptosis and exhibited potent antitumor activity and [67].

The synthesis of substituted compounds 75a-i has been accomplished as outlined in Scheme 8.



Scheme 8: Synthesis of pyrazole derivatives 75a–i: (a). K2CO3/ CH3CN reflux; (b). NH2NH2/H2O, CH3OH reflux Where: R1 = H, Cl, OMe; R2 = H, t-Bu, Cl;

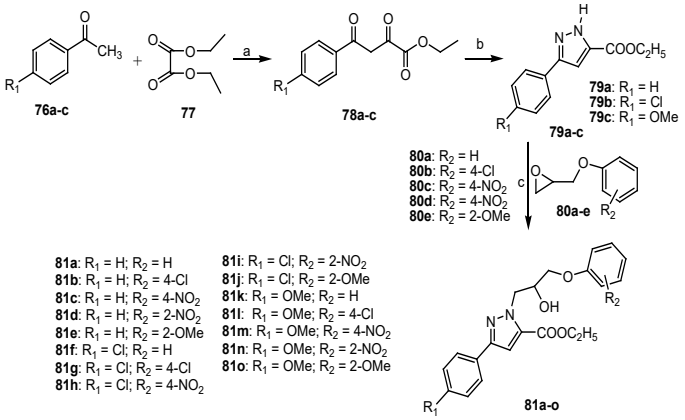
Lung cancer is common, with some arylpyrazole derivatives known to inhibit A549 cell growth.

Synthesis of substituted ethyl 1-(2'-hydroxy-3'-aroxypropyl)-3-aryl-1H-pyrazole-5-carboxylate 81a-o is described in Scheme 9. Compounds of substituted ethyl 3-aryl-1H-pyrazole-5-carboxylate 79a-c, were obtained from corresponding ethyl 2,4-dioxo-4-arylbutanoate 78a-c, which was prepared using substituted acetophenones 76a-c and diethyl oxalate 77, and hydrazine in the presence of acetic acid at room temperature (Scheme 9).

The ethyl 1-(2'-hydroxy-3'-aroxypropyl)-3-aryl-1*H*-pyrazole-5-carboxylate 81a-o were prepared from ethyl 3-aryl-1*H*-pyrazole-5-carboxylate 79a-c with substituted 2-aryloxy methylepoxide 80a-e. The reaction occurred in the presence of potassium carbonate at refluxing in acetonitrile, with moderate yields and completely regioselectivity [68].

Ethyl-1-(2'-hydroxy-3'-aroxypropyl)-3-aryl-1*H*-pyrazole-5-carboxylate derivatives were synthesized for highlighting the anti-tumor activity. Compound 81i was the most effective in suppressing A549 (adenocarcinomic human alveolar basal epithelial cell) growth (IC_{50} = 26 µM) [68].

A few 1-(2'-hydroxy-3'-aroxypropyl)-3-aryl-1*H*-pyrazole-5-carbohydrazide derivatives had been investigated for their primary cytotoxic activity against A549 lung cancer cell line [70]. Compound 1-(3'-(4'-chlorophenoxy)-2'-hydroxypropyl)-3-(4'-chlorophenyl)-1*H*-pyrazole-5-carbohy-drazide had the most autophagy inducing effect in NCI-H460 lung cancer cells [71].



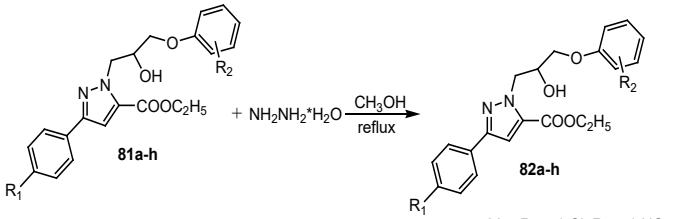
79a: R_1 = H
79b: R_1 = Cl
79c: R_1 = OMe

80a: R_2 = H
80b: R_2 = 4-Cl
80c: R_2 = 4-NO_2
80d: R_2 = 4-NO_2
80e: R_2 = 2-OMe

81a: R_1 = H; R_2 = H
81b: R_1 = H; R_2 = 4-Cl
81c: R_1 = H; R_2 = 4-NO_2
81d: R_1 = H; R_2 = 2-NO_2
81e: R_1 = H; R_2 = 2-OMe
81f: R_1 = Cl; R_2 = H
81g: R_1 = Cl; R_2 = 4-Cl
81h: R_1 = Cl; R_2 = 4-NO_2
81i: R_1 = Cl; R_2 = 2-NO_2
81j: R_1 = Cl; R_2 = 2-OMe
81k: R_1 = OMe; R_2 = H
81l: R_1 = OMe; R_2 = 4-Cl
81m: R_1 = OMe; R_2 = 4-NO_2
81n: R_1 = OMe; R_2 = 2-NO_2
81o: R_1 = OMe; R_2 = 2-OMe

Scheme 9: Synthesis of substituted ethyl 1-(2'-hydroxy-3'-aroxypropyl)-3-aryl-1H-pyrazole-5-carboxylate 22a-c. a. K2CO3 / CH3CN 81°C, 15-18h, 54-93% yields.

The 1-(2'-hydroxy-3'-aroxypropyl)-3-aryl-1*H*-pyrazole-5-carbohydrazides compounds 82a-h were obtained (Scheme 10) from ethyl 1-(2'-hydroxy-3'-aroxypropyl)-3-aryl-1*H*-pyrazole-5-carboxylate 81a-h with hydrazine hydrate [69].

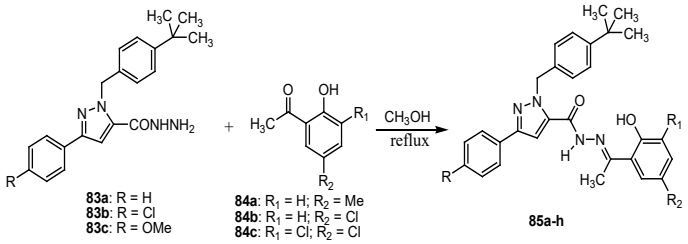


82a: R_1 = H; R_2 = Cl
82b: R_1 = H; R_2 = 4-NO_2
82c: R_1 = H; R_2 = 2-OMe
82d: R_1 = 4-Cl; R_2 = 4-Cl
82e: R_1 = 4-Cl; R_2 = 4-NO_2
82f: R_1 = 4-Cl; R_2 = 2-OMe
82g: R_1 = 4-OMe; R_2 = 4-Cl
82h: R_1 = 4-OMe; R_2 = 4-Cl

Scheme 10: Synthesis of 1-(2'-hydroxy-3'-aroxypropyl)-3-aryl-1H-pyrazole-5-carbohydrazide.

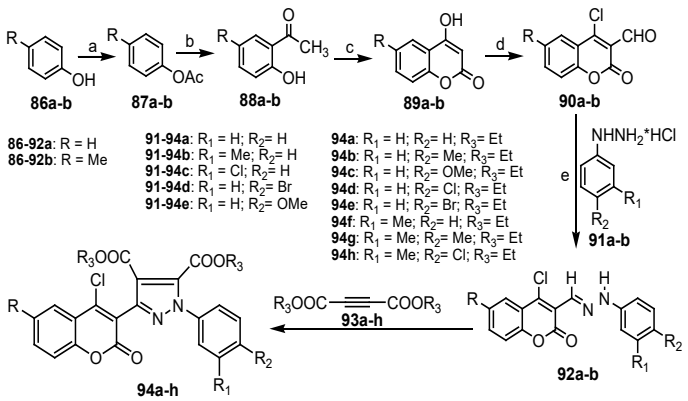
The synthesis of 3-aryl-1-(4-*tert*-butylbenzyl)-1*H*-pyrazole-5-carbohydrazide hydrazone derivatives 85a-h has been accomplished as outlined in Scheme 11 starting from 3-aryl-1-(4-*tert*-butylbenzyl)-1*H*-pyrazole-5-carbohydrazide 83a-c with substituted 1-(2-hydroxyphenyl)ethanone 84a-c [70].

1-(4-*tert*-Butylbenzyl-N'-(1-(5-chloro-hydroxyphenyl) ethylidene)-3-(chlorophenyl)-1*H*-pyrazole-5-carbohydrazide 85c displayed IC_{50}=0.28 µM and induced apoptosis of A549 lung cancer cells [71].



Scheme 11: Structure of substituted 1H-pyrazole-5-carbohydrazide hydrazone 85a-h.

Novel pyrazole derivatives were synthesized by Kumar et *al.* compounds 94a-h were evaluated against human tumor cells lines, some compounds showed high anticancer activity, while doxorubicin used as reference drug [72]. 4-Chloro-3-formylcoumarins 90a,b were obtained by acetylation starting from substituted phenols 86a,b (Scheme 12). with acetyl chloride gives 87a,b. Subsequent by Fries rearrangement with $AlCl_3$ were obtained the compounds 88a,b. 4-Hydroxycoumarins 89a,b. were prepared by annulation reaction of 80a,b with diethyl carbonate in presence of NaH. Formylation of 89a,b with DMF/$POCl_3$ under Vilsmeiere-Haack conditions afforded 90a,b compounds. Condensation of 4-chloro-3-formylcoumarin 90a,b with phenylhydrazines hydrochloride 91a-e in methanol solvent in presence of AcOH and H_2O medium afforded the corresponding 2*H*-chrome nophenylhydrazone 92a-h. Cycloaddition of 93a-h with diethyl but-2-yn-edioate afforded corresponding 2-oxo-2*H*-chromenylphenyl-1*H*-pyrazole-4,5-dicarboxylate 94a-h compou nds [72].



Scheme 12: Synthesis of compounds 94a-h.: (a). AcCl, Py, DCM; (b). AlCl3, 1200C; (c). NaH, diethyl-carbonate; (d). POCl3 DMF; (e). MeOH, AcOH:H2O; f. diethyl but-2-ynedioate, 1300C.

Exposure of cells to stress, such as heat shock or oxidative stress, results in the accumulation of molecular chaperones, commonly known as heat shock proteins (Hsp). Hsp90 has emerged over the last few years as being the particular interest, because of its role in the evolution, development, and disease pathology of cancer [73].

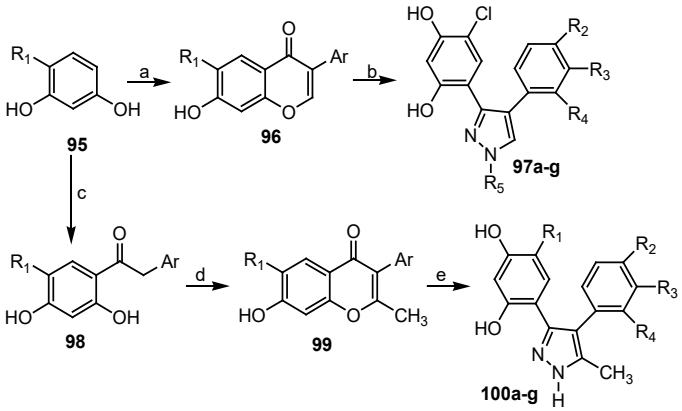
The chromen-4-ones 96 and 99 were synthesised from phenylacetic acids by one of two methods depending on whether the substituent at the 5-position of the pyrazole was hydrogen 97a–g or a methyl group 100a–d (Scheme 13) [73].

Small molecule Hsp90 inhibitors have found by the Cheung et *al*. [74]. Pyrazole derivatives have been shown to have selective anti-proliferative action on many human cancer cells and promise to be inhibitors of cell proliferation.

Inspired by the many successful applications of hybrids in general, coumarin and pyrazole nuclei have been incorporated, obtaining powerful new drugs with potential anticancer action. [74]. Wu et *al.* synthesized the coumarin-pyrazole hybrid which demonstrated the significant anti-proliferative effect on human cancer cells HepG2 [74]. Encouraged by the aforementioned results, Hong Dai et al. they further studied the hybrids of coumarin and pyrazole oxime in the hope of finding effective antitumor and metastatic agents.

New coumarin/pyrazole oxime hybrids 110a-v are prepared and assessed for the anticancer and anti-metastatic effects systematically [75]. Scheme 14 presents the synthesis of coumarino-pyrazole hybrid compounds 110a-v.

Firstly, intermediate 101 was treated with compound 102 under acidic condition to form intermediate 103. Then compound 103 was condensed with dibromoalkane at room temperature to get compounds 104a,b in good yields.

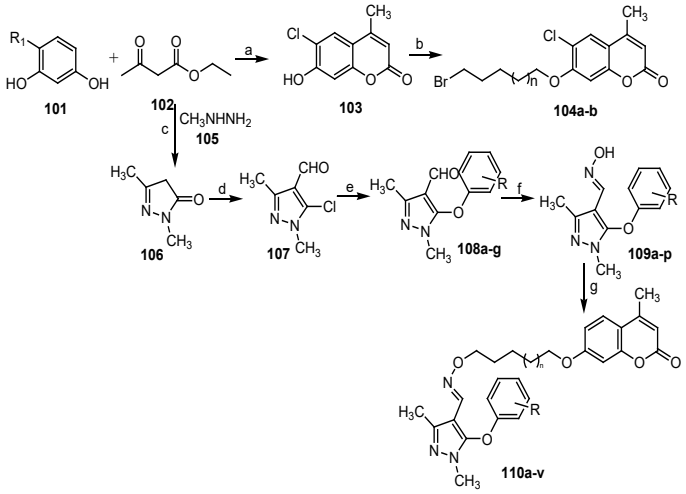


	R_1	R_2	R_3	R_4	R_5
a	Et	OCH_2CH_2O	OCH_2CH_2O	H	H
b	Cl	OCH_2CH_2O	OCH_2CH_2O	H	H
c	Cl	H	H	H	H
d	Cl	OC_3H_6CN	H	H	H
e				OC_3H_6CN	H
f				H	H
g				H	Me

Scheme 13: (a). One pot a. ArCH2CO2H, BF3 OEt2, PCl5, DMF; (b). hydrazine hydrate (or methyl hydrazine 39g, EtOH, reflux; (c). ArCH2CO2H, BF3 OEt2, 800C, 90 min; (d). K2CO3, acetic anhydride, DMF, reflux, 6 h; e. hydrazine hydrate, EtOH, reflux.

The reaction of compound 102 with 40% methylhydrazine 105 gave compound 106 readily, which was further treated with $POCl_3$ and DMF at 100^{0}C to produce intermediate 107. Compound 107 was reacted with various substituted phenols using NaOH as alkali to afford the corresponding carbaldehydes 108a-g. Subsequently, compounds 108a-g were treated with hydroxylamine using KOH as alkali to generate the important intermediates oximes 109a-p in good yields. Finally, the target compounds 110a-v were prepared in satisfactory yields by the reaction of oximes 109a-p with compounds 104a,b, with potassium carbonate and cesium carbonate in CH_3CN at reflux [76].

Some of these hybrids exhibited good *in vitro* anti-proliferative potency on the tested human cancer cells. Especially, compound 110n had the highest cell growth inhibitory effects which was comparable to 5-FU and ADM, while it showed little effect upon the proliferation of non-tumor LO2 cell lines at similar dosage. 5-FU and ADM, two of the first-line drugs, were selected as standard anticancer agents for comparisons [77,78].



	R		R		
n = 1	a 3-F b 4-F c 4-Cl d 4-Br e 4-I f 4-Me	n = 2	g 2-F h 3-F i 4-F j 2-F,3-F k 2-F,4-F l 3-F, -F	m 3-Cl n 4-Cl o 2-Br p 3-Br q 4-Br s 2-Me	t 4-Me u 3-CF_3 v 4-OCF_3

Scheme 14: Preparation of compounds 110a-v. (a). concentrated sulfuric acid, 0 0C, 3h, 82%; (b). dibromoalkane, K2CO3, DMF, rt, 10h, 75-78%; (c). 60 0C, 1h, reflux, 6 h, 82%; (d). POCl3, DMF, 100 0C, 5h, 80%; (e). ArOH, sodium hydrate, ethanol, reflux, 3h, dimethyl sulphoxide, 100 0C, 8-16 h, 53-70%; (f). NH2OH.HCl, potassium hydroxide, methanol, reflux, 6-20h, 55-73%; g. compounds 104a,b, K2CO3, Cs2CO3, CH3CN, reflux, 18-26h, 56-70%.

Conclusion

The pyrazole nucleus occupies an important place in the development of bioactive molecules, being a very good pharmacological agent.

In this book chapter we set out to present strategies for the synthesis of pyrazole derivatives, with antibacterial and antitumor activity.

The very good results presented represent a starting point in the development of bioactive pyrazole compounds and not only those hybrids, with superior properties to simple derivatives.

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