Pyrazoles as Promising Scaffold for the Synthesis of Anti-Inflammatory and/or Antimicrobial Agent: A Review

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Abstract: There has been a considerable interest in the development of novel compounds with anti-inflammatory and /or antimicrobial activities. Several economical and social merits have been prospected for compounds with dual effects. Pyrazoles are an important class of compounds for new drug development that attracted much attention. Several pyrazole derivatives have been synthesized as target structures and evaluated for their biological activities. This review describes the synthesis and the development of new pyrazoles that possess anti-inflammatory and /or antimicrobial activities. The cytotoxicity of the reported compounds indicates good safety associated with many of the pyrazole derivatives. However, the need for standardized method for cytotoxicity evaluation is required for better understanding of the compounds safety and the safety-structure relationships.

Keywords: Pyrazole derivatives, anti-inflammatory agents, antimicrobial agents.

INTRODUCTION

Pyrazole refers to a class of simple aromatic ring organic compounds of the heterocyclic series characterized by a 5-membered ring structure composed of three carbon atoms and two nitrogen atoms in adjacent positions. Pyrazole and fused heterocyclic pyrazole derivatives constitute an interesting class of heterocycles due to their synthetic versatility and effective biological activities [1]. This gave a great impetus to the search for potential pharmacologically active drugs carrying pyrazole scaffold.

Numerous compounds containing the pyrazole moiety were found to exhibit wide range of biological activities such as *Herpes simplex* virus inhibitor activity [2], analgesic [3], apoptosis-inducing activity [4], MAP kinase inhibitory [5], monoamine oxidase inhibitory activities [6], anticancer [7], anti-HIV [8], anti-proliferative [9], hypnotic [10], anti-arrhythmic [11], antimalarial [12], anti-leishmania [13], psychoanaleptic [14], anticonvulsant [15], anti-inflammatory [16] and antimicrobial [17] activities. Among these, the present review will focus on the anti-inflammatory and / or antimicrobial activity of pyrazole derived compounds.

Fast and effective relief of pain and inflammation in human beings is continued to be a major challenge for medical researchers. Non-steroidal anti-inflammatory drugs (NSAIDs) are important therapeutic agents for the alleviation of pain and inflammation associated with a number of pathological conditions [18]. A major mechanism of action of NSAIDs is lowering prostaglandin (PG) production through the inhibition of cyclooxygenase (COX); a key enzyme in PGs biosynthesis that catalyses the conversion of arachidonic acid into PGs and thromboxanes [19].

COX inhibition may also elicit an increase in 5-lipoxygenase activity that would potentiate the production of leukotriene-B4 (LTB4) and vasoconstrictor peptidoleukotrienes by the lipoxygenase pathway, and this can contribute to vascular and other mucosal damage induced by NSAIDs [20, 21]. PGE2 and LTB4 play an important role in mediating inflammation and other biological processes. For example, PGE2 *via* its receptor-mediated activity [22] elicits fever and pain in inflammation, and LTB4 is a potent chemotactic factor [23]. Furthermore, PGE2 and LTB4 stimulate enzymatic cartilage degradation in joints [24].

Because PGs have dual function; mediation of inflammation and cytoprotection in the stomach and intestine; long term usage of non-selective NSAIDs to relieve the symptoms of inflammation and pain always results in gastrointestinal (GI) damage, ulceration, haematologic effects and nephrotoxicity [25]. Thus, long term use or high intake of traditional NSAIDs can lead to severe side effects [26-29] and cause significant number of mortality among their dependent users [30]. A major breakthrough in anti-inflammatory re-

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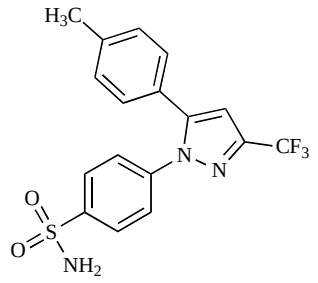
search occurred when it was discovered that COX exists in three isoforms COX-1, COX-2 and COX-3 which are regulated differently. The discovery of the inducible isoform COX-2 spurred the search for novel anti-inflammatory agents devoid of the undesirable effects associated with classical non selective NSAIDs.

Three COX-2 selective inhibitors, celecoxib (**1**) [31], rofecoxib (**2**) [32] and valdecoxib (**3**) [33], are currently prescribed for the treatment of arthritis and inflammatory diseases. These drugs show anti-inflammatory activity with reduced GI side effects. Although relieving pain and inflammation at least as effectively as standard NSAIDs, the above COX-2 selective inhibitors fail to inhibit LT biosynthesis and they do not ameliorate any potentially adverse downstream effects of the LTs, e.g. activation on cartilage-destroying enzymes by tumour necrosis factor-α(TNF-α) and interleukin-1β(IL-1β) [24]. In fact, experimental and clinical studies reported that COX-2 selective inhibitors can aggravate pre-existing gastric damage [34].



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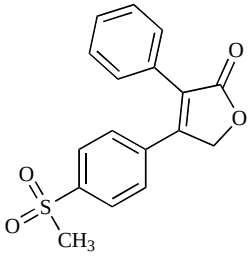

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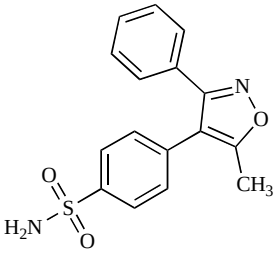

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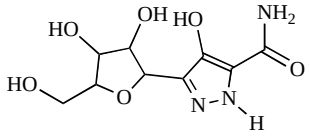
Among the above COX-2 inhibitors that encompass a pyrazole nucleus, celecoxib, 4-[5-(4-methylphenyl)-3-(trifluorophenyl)-1H-pyrazol-1-yl]benzenesulphonamide, occupies a unique position as a potent and GI safe anti-inflammatory and analgesic agent. It is considered as a typical model of the diaryl heterocycles template that is known to inhibit selectively the COX-2 enzyme [35].

The dramatically rising prevalence of multi-drug resistant microbial infections in the past few decades has become a serious health care problem. The search for new antimicrobial agents will consequently always remain an important and challenging task for medicinal chemists. The concomitant use of several drugs to treat microbial infections and inflammatory conditions that might be associated with the infections may cause health problems especially in patients with impaired liver or kidney functions [18]. Therefore, the development of dual acting drugs, prossesing anti-inflammatory and antimicrobial activities, would have an advantage of reducing the number of drugs used for these conditions and would have a better patient compliance. The discovery of the natural pyrazole C-glycoside pyrazofurin (**4**) and its antimicrobial activity [36] draw much attention towards the use of pyrazoles as a scaffold for anti-inflammatory and antimicrobial agents.



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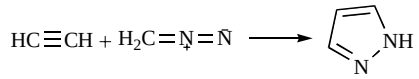
SYNTHESIS OF PYRAZOLE NUCLEUS

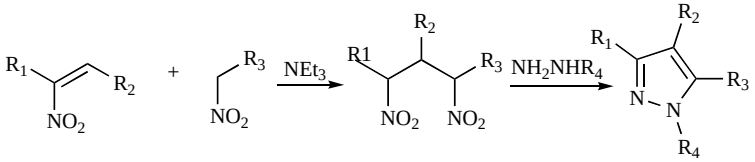
A number of methods to synthesize pyrazole derivatives have been reported. Pyrazoles can be formed from acetylenes and diazomethane (Scheme **1**) [37].



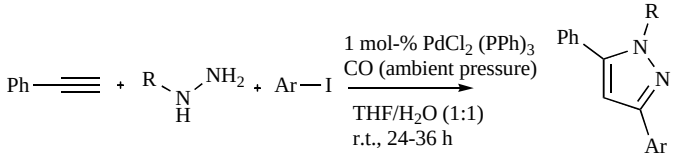
Scheme 1. Formation of pyrazoles from acetylenes and diazomethane.

Aliphatic nitro compounds have proved to be useful starting materials in organic synthesis. When the nitro compounds are properly substituted they can cyclise, yielding heterocyclic compounds (Scheme **2**) [38].

Pyrazole or isoxazole derivatives are readily prepared by a palladium-catalysed four-component coupling of a terminal alkyne, hydrazine (hydroxylamine), carbon monoxide under ambient pressure, and an aryliodide (Scheme **3**) [39].



Scheme 2. Synthesis of pyrazole from nitro compounds.



Scheme 3. Terminal alkyne coupling synthesis of pyrazole.

A general, highly flexible Cu-catalysed domino C-N coupling/hydroamination reaction constitutes a straight forward alternative for an existing methodology for the preparation of pyroles and pyrazoles (Scheme **4**) [40].

A highly regioselective synthesis of 1-aryl-3,4,5-substituted pyrazoles based on the condensation of 1,3-diketones with arylhydrazines proceeds at room temperature in *N,N*-dimethylacetamide and furnishes pyrazoles in good yields (Scheme **5**) [41].

1,3-Diketones, which were synthesised *in situ* from ketones and acid chlorides, were converted into pyrazoles by the addition of hydrazine. This method allows a fast and general synthesis of previously inaccessible pyrazoles and synthetically demanding pyrazole-containing fused rings (Scheme **6**) [42].

A regioselective one-pot synthesis of substituted pyrazoles from *N*-monosubstituted hydrazones and nitroolefins gives products in good yields. A key nitropyrazolidine intermediate was characterised and a plausible mechanism was proposed (Scheme **7**) [43].

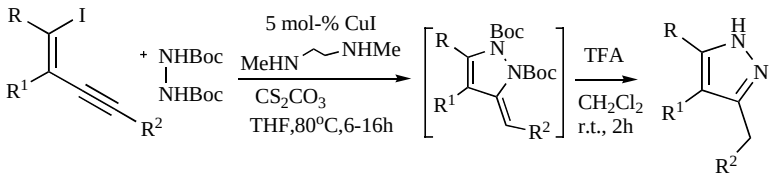
One-pot synthesis of pyrazole-5-carboxylates by cyclisation of hydrazone 1,4-dianions with diethyl oxalate also has been reported. The cyclisation of hydrazone dianions with diethyl oxalate afforded pyrazole-5-carboxylates (Scheme **8**) [44].

BIOLOGICAL ACTIVITY

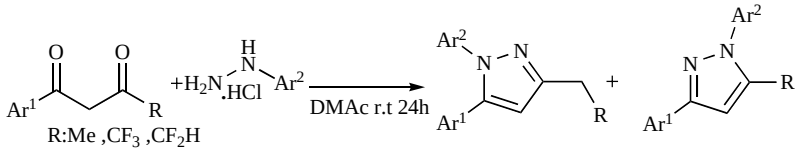
1. Anti-Inflammatory

Having considered briefly the difficulties in rationale, the complexities to find an anti-inflammatory agent will be discussed. Unfortunately, most experimental animals do not suffer from connective tissue diseases. However, pharmacologists are forced to employ animal models, hoping that their findings in experimental animals, inflicted under various conditions, simulating certain phases of the inflammatory process and response may become applicable to man [45].

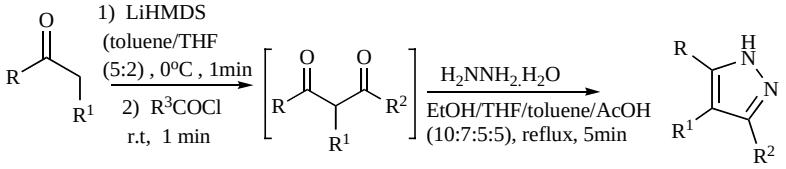
A whole battery of tests, both acute and chronic, are normally employed to evaluate potential anti-inflammatory drugs. Some of the acute screening tests are: Ultraviolet-erythema test in guinea pigs, carrageenan oedema test in rats and anti-bradykinin test in guinea pigs. Some of the commonly employed chronic tests are: Non-established and established adjuvant arthritis test and cotton pellet granuloma test in rats [46].



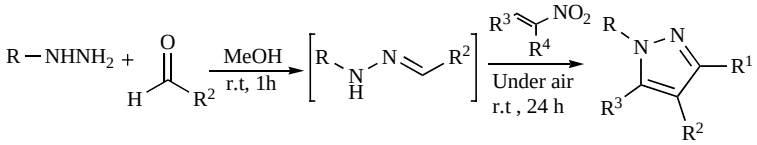
Scheme 4. Cu-catalyzed synthesis of pyrazoles.



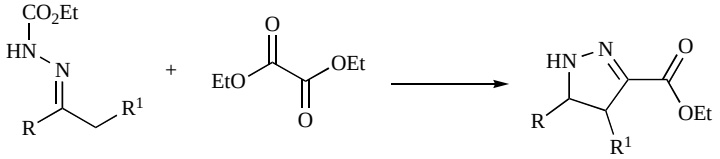
Scheme 5. Synthesis of pyrazoles from condensation of diketones.



Scheme 6. Synthesis of pyrazoles in situ from ketones.

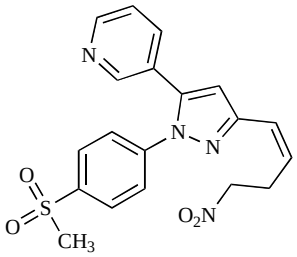


Scheme 7. One pot synthesis of pyrazoles from *N*-monosubstituted hydrazones and nitroolefins.



Scheme 8. One pot synthesis of pyrazoles by cyclization of hydrazone 1,4-dianions.

1-(Methylsulfonyl)-5-(3-pyridyl)-disubstituted pyrazolyl compound (**5**) showed moderate COX-2 inhibition in human whole blood (HWB) assay and only modest COX-1 inhibition at a high concentration (55% inhibition at 100 μM concentration).



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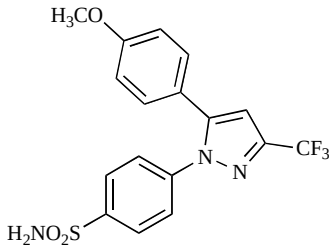
Some interesting features can be deduced from the comparison of compound (**5**) structure with that of celecoxib. The sulfonamide group present in celecoxib was replaced by methylsulfonyl group, which is believed to be crucial for increasing the COX-2 selectivity [46]. The 4-methylphenyl group at 5-position of the pyrazole ring was replaced by a 3-pyridyl substituent. The trifluoromethyl group in celecoxib was replaced by an NO-donor group. This change in substitution opens up an additional space that was proven to be important for the binding of selective COX-2 inhibitors, yet the steric requirement by the enzyme for the inhibitor remained critical [47].

Structurally diverse 1, 5-diaryl pyrazoles (**6**) were also investigated for COX-2 inhibitory activity [48]. The resulted contour maps gave rationale for the COX-2 inhibitory profile of the structurally diverse 1,5-diaryl pyrazoles. The fact that the 3-D QSAR model did not project any colour contour in the region occupied by the $SONH_2$ group provides rationale for designing non-sulfonyl COX-2 inhibitors [49] that might circumvent the problem of side effects associated with the $SONH_2$ group.

Accordingly, compound (**6**) is useful for the design of novel selective COX-2 inhibitors.



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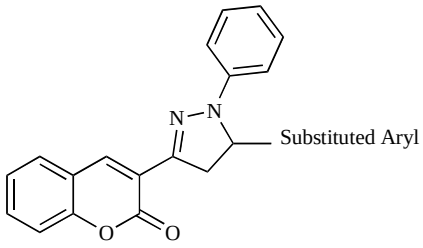
Preliminary *in vivo* screening of biological activities for biheterocyclic compounds (**7**) containing both coumarin and pyrazoline ring systems, showed anti-inflammatory activity of 56.7 % inhibition in carrageenan-induced rat paw oedema, when the substituted aryl was 2,4-$(Cl)_2$-C_6H_3 [50].

The pyrazoline derivatives (**8**) having 2,4,6-trimethoxy group in the phenyl ring at C-5 of pyrazoline nucleus were found to posses 80.70 ± 3.23 % inhibition [51].

Celecoxib analogues that possess a N-hydroxypyrid-2(1H) one (**9**), with 5-lipoxygenase pharmacophore acted as dual inhibitors of cyclooxygenases and 5-lipoxygenase with IC_{50} = 0.35l M, ED_{50} = 66.9 mg/kg p.o in a carrageenan-induced rat paw oedema assay [52].



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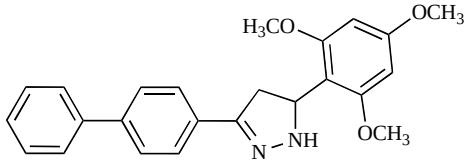

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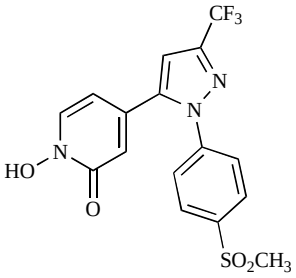
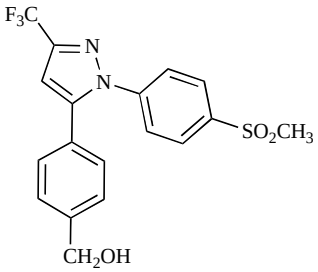


9

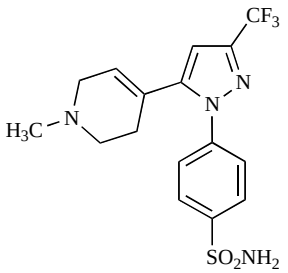
Other studies indicated that hybrid ester nitric oxide-releasing anti-inflammatory prodrug (NONO-coxibs) constitutes a plausible drug design concept targeted towards the development of selective COX-2. The 5-(4-hydroxymethylphenyl)-1-(4-aminosulfonylphenyl)-3-trifluoromethyl-1H-pyrazole (**10**), exhibited ED_{50} range of 77.1 to 111.6 μmol/kg p.o in a carrageenan-induced rat paw oedema assay [53].



10

Additionally, the 4-[5-(1-methyl-1,2,3,6-tetrahydropyridin-4-yl)-3-trifluoromethylpyrazol-1-yl]benzenesulfonamide (**11**); showed an ED_{50} of 61.2 mg/kg p.o inhibitory activity in a carrageenan-induced rat paw oedema assay [54].

Moreover 1-(4-methanesulfonylphenyl)-5-aryl-1H-pyrazol-3-carboxylic acid (**12**) showed ED_{50} of 85.2 mg/kg inhibitory activity in a carrageenan-induced rat paw oedema assay [55].



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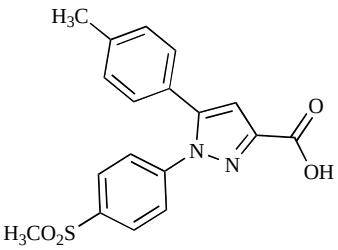
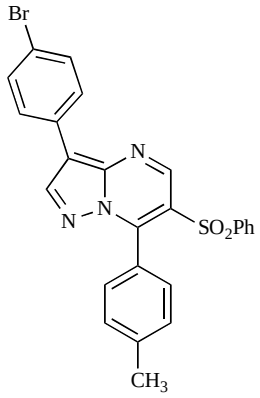


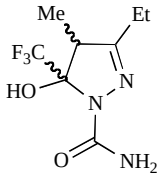
12

The fused pyrazole derivative 2-(4-bromophenyl)-6-(phenylsulfonyl)-7-(4-methylphenyl)-pyrazolo[1,5-a]pyrimidine (**13**) showed 74.1 % oedema inhibition in rat paw model system [56].



13

The microwave-assisted synthesis of 5-trifluoromethyl-4,5-dihydro-1H-pyrazole (**14**) exhibited 43.7±8.1% inhibition in carrageenan-induced inflammation [57].



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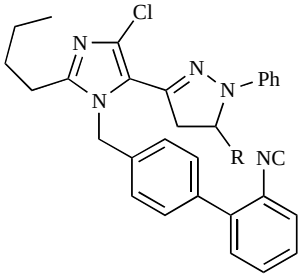
2. ANTIMICROBIAL ACTIVITY

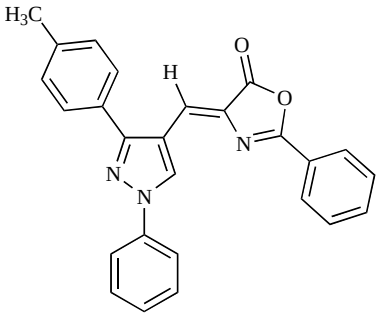
An antimicrobial is a substance that kills or inhibits the growth of microbes such as bacteria, fungi, or viruses. Antimicrobial drugs either kill microbes (microbicidal) or prevent the growth of microbes (microbistatic). A number of methods are commonly described for antimicrobial studies, e.g. the agar diffusion method, cup-plate method and microdilution method [58, 59], that used different test strains: *Bacillus substilis, Escherichia coli, Pseudomonas fluorescens, Xanthomonas campestris pvs, Xanthomonas oryzae, Aspergillus niger, Aspergillus flavus, Fusarium oxysporium, Trichoderma species, Candida albicans* and others.

4,5-Dihydro-3-(substituted-imidazole)–5-substituted-1-phenyl-1H-pyrazoline derivatives were synthesized and their antimicrobial activity has been evaluated. Compounds **15a** had MIC of 17,12,13,10 and 11 and **15b** exhibited MIC of 18, 14, 12, 12 and 14 μg mL^{-1} against *B. substilis, E. coli, P. fluorescens, X. campestris pvs, X. oryzae,* respectively [60].



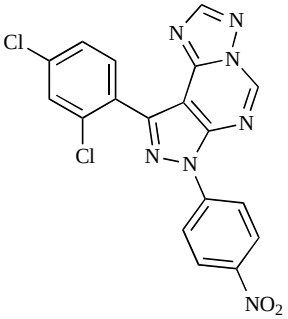
R= **15a**, CH_2Cl
15b, CH_2Br

The pyrazole containing 2,4- disubstituted oxazole ring system represents a new class of pharmacophore for the broad spectrum antimicrobial activity. Compound (**16**), at 30 μg/mL concentrations showed a 7.2, 7.0 and 7.2 mm zone of inhibition against *E. coli, P. aeruginosa and S. aureus*, respectively. This compound also showed antifungal activity at higher concentrations (60 μg/mL) against *Candida albicans* [61].



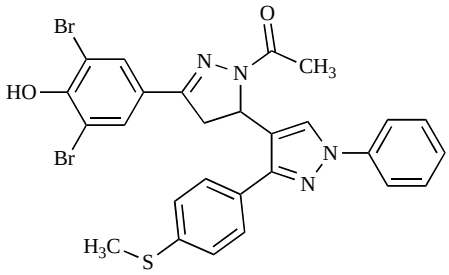
16

Some fused pyrazoles derivatives (**17**) exhibited a 13, 13 and 12 mm inhibition zone diameter against *E. coli, S. aureus* and *C. albicans,* respectively, at a concentration of 20 mg/ml [62].



17

Acetyl-diphenyl-dihydro-pyrazole derivative (**18**) showed 13, 17, 16, 19 and 17 mm inhibition zone diameter against *B. coccous, B. subtilis, E. coli, P. vulgaris* and *A. niger* at a concentration of 40 μg/mL [63].



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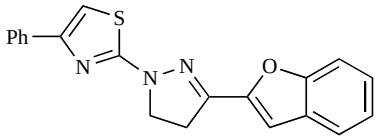
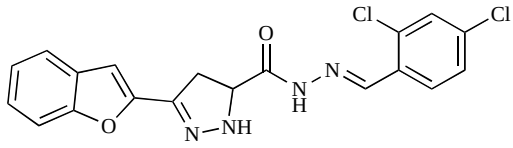
1-(Thiazol-2-yl)pyrazoline (**19**) showed 17 mm zone of inhibition activity against *S. aureus* and 25 mm zone of inhibition against *E. coli* at 100 μg/mL [64].



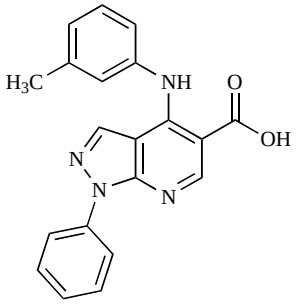
19

The 3-Substituted 5-(benzofuran-2-yl)-pyrazole derivatives (**20**) had antimicrobial activity of 40, 40 and 30 mm inhibition zone against *E. coli*, *B. subitilis* and *C. albicans,* respectively [65].



20

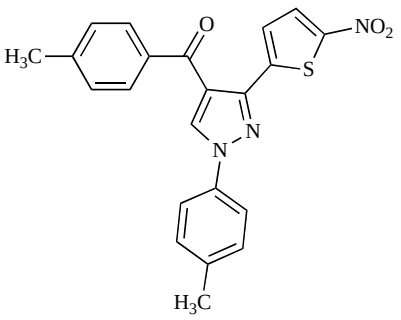
The 1H-pyrazolo[3,4-b]pyridine and thieno[2,3-b]pyridine derivatives (**21**) show 64 MIC (μg/mL) antibacterial profile against a drug-resistant *Staphylococcus epidermidis* clinical strain [66].



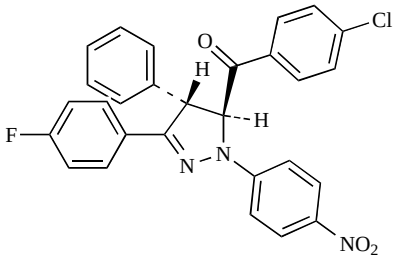
21

A series of pyrazoles namely 1-aryl-3-(5-nitro-2-thienyl)-4-aroyl pyrazoles (**22**) has been synthesized and screened for their antibacterial and antifungal activities. A 0.125 μg/mL was shown to be effective MIC against *S. aureus, E. coli, P. aeruginosa, B. subtilis* and *C. albicans* [67].

Pyrazoline and pyrrolo[3,4-c]pyrazole-4,6-dione derivatives (**23**) at a concentration of 20 mg/mL exhibited antimicrobial activity of 12, 12 and 10 mm inhibitory zone against *E. coli, S. aureus and C. albicans*, respectively [68].

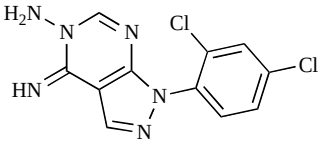


22



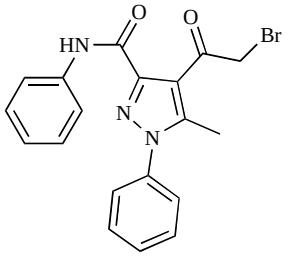
23

Also the fused pyrazolo[3,4-d]-pyrimidine and pyrazolo[4,3-e][1,2,4]-triazolo[1,5-c]pyrimidine derivative **(24)** at a concentration of 20 mg/mL showed antimicrobial activity against *E. coli, S. aureus and C. albicans* of 13, 13, 12 mm inhibition zone, respectively [62].



24

The N-phenylpyrazole derivative 4-(2-bromoacetyl)-5-methyl-1-phenyl-3-phenylcarbamoyl-1H-pyrazole (**25**) at a concentration of 0.05 mg/mL has shown antimicrobial activity of 18±3, 20±1.3, 12±0.5, 16±1.2 mm inhibition zone diameter against *S. aureus, P. aeruginosa, A. fumigates* and *C. albicans,* respectively [69].



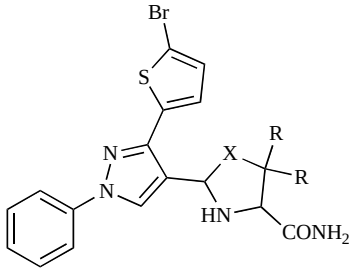
25

3. ANTI-INFLAMMATORY AND ANTIMICROBIAL ACTIVITY

A number of pyrazole derivatives with anti-inflammatory and antimicrobial activity were designed and synthesised. Compound **26b** had a 8.97 ED_{50} [μmol], which is comparable to that of indomethacin, and MIC of 50, 25

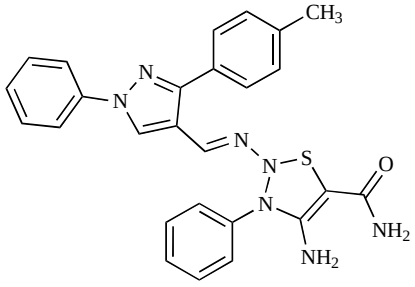
(about 50% of that found for ampicillin) and >200 μgmL^{-1} to *E. coli, S. aureus* and *C. albicans,* respectively, proved to be an active anti-inflammatory-antimicrobial agent with no ulcerogenic effect and good safety margin compared to compounds **26a** and **26c** [70].

26	R	X
a	H	O
b	H	S
c	CH_3	S



26a-c

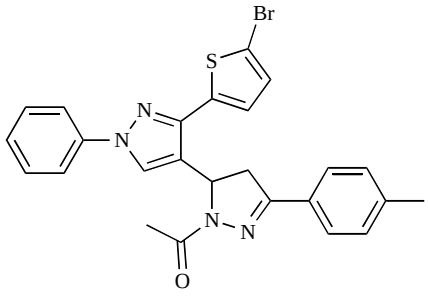
In addition, compound **27** revealed a remarkable anti-inflammatory activity (COX-2 IC_{50} = 1.30 μM), COX-1 IC_{50} (>100 μM)) which is comparable to that of indomethacin in both local and systemic *in vivo* bioassays at the same dose level. Meanwhile, these compounds displayed more distinct *in vitro* inhibitory activity against COX-2 than COX-1 when compared to indomethacin. These findings substantiate the idea that the anti-inflammatory activity of such type of compounds might be attributed to the selective inhibition of the COX-2 rather than the COX-1 enzyme.



27

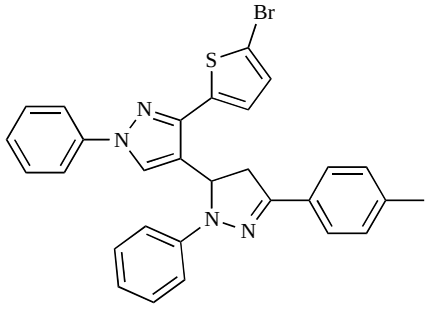
Compound (**27**) also showed pronounced antibacterial activities (MIC of 50, 12.5 and >200 μg/mL against *E. coli, S. aureus* and *C. albicans,* respectively) comparable to ampicillin against Gram positive and Gram negative bacteria [71]. Therefore, such compound would represent a fruitful matrix for the development of a new class of dual nonacidic anti-inflammatory-/antimicrobial agents that deserves further investigation.

The activities of compounds **28** (COX-2 IC_{50} = 1.32μM; COX-1 IC_{50} = >84.71 μM) and **29** (COX-2 IC_{50} = 0.37μM; COX-1 IC_{50} = >100 μM) were capable of modulating the inflammatory response and were assumed to have *in vivo* anti-inflammatory activity similar to that of indomethacin. These compounds also showed minimum ulcerogenic activity compared to phenylbutazone and indomethacin. Meanwhile, these compounds displayed distinct *in vitro* inhibitory activity against COX-2 than COX-1 compared to indomethacin and celecoxib.



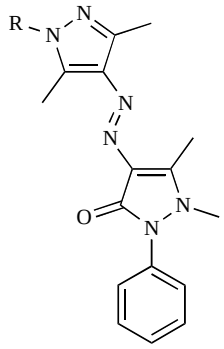
28

On the other hand, compounds **28** (MIC 200 and 25 μg/mL) and **29** (MIC 50 and 12.5 μg/mL) showed moderate antimicrobial activity against *E. coli* S *S. aureus,* respectively [72].



29

Compound (**30**) is another pyrazole derivative that proved to be active anti-inflammatory and antimicrobial agent.



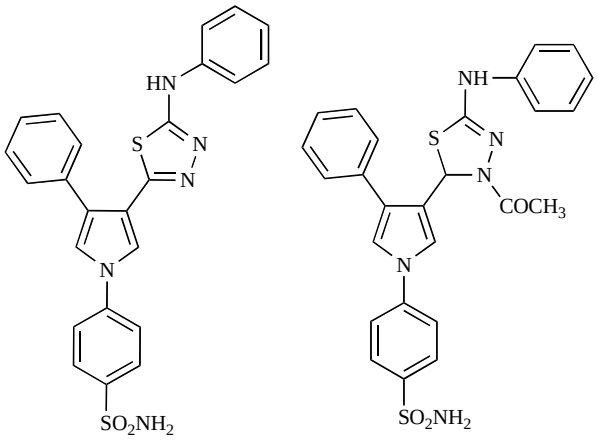
R=p-(H_2NSO_2)-C_6H_4

30

Its anti-inflammatory activity was comparable to that of indomethacin (ED_{50} = 8.96 μmol), without ulcerogenic effect or toxicity up to 300 mg/kg when given orally. In addition, its antibacterial activity against *E. coli* was comparable to that of ampicillin, while its activity against *S. aureus* was about 50% that of ampicillin [73].

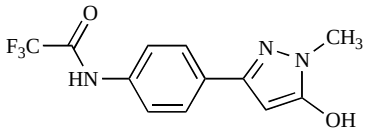
Recently, the pyrazolo benzene sulfonamide derivatives **31** and **32** were found to be potent anti-inflammatory agents. These compounds (**31** and **32**) displayed selective inhibitory activity towards COX-2 with IC_{50} of 0.43 ± 0.04 and 0.51 ± 0.06 μM which is more potent than indomethacin (IC_{50} 2.63

± 0.02 μM). Also, these compounds exhibited promising MIC of 50, 12.5, >200 μg/mL (**31**) and 50, 25, >200 μg/mL (**32**) against *E. coli*, *S. aureus* and *C. albicans*, respectively [74].



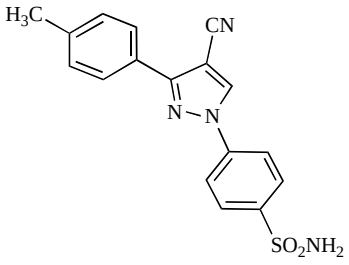
31 **32**

The hydroxypyrazole derivative (**33**) possessed an ED_{50} of 8.34 μmol as anti-inflammatory agent with no detectable ulceration. The compound exhibited high antimicrobial activity against *E. coli*, *S. typhimurium*, *S. aureus*, *B. subtilis and C. albicans*, with MIC of 50, 50, 100, 200 and 200 μg/mL, respectively [75].



33

The pyrazolyl benzenesulfonamide derivative **34** exhibited dual anti-inflammatory, COX-2 IC_{50} (0.92 ± 0.02 μM), COX-1 IC_{50} (94.22 ± 0.18 μM) and antimicrobial activity against *E. coli*, *S. aureus* and *C. albicans* with MIC of 25, 25 and 200 (μg/mL), respectively [76].



34

Cytotoxic Effects of Pyrazole Derivatives

Because of the continuous interest in pyrazole derivatives [77], cytotoxicity investigations of newly synthesised compounds have been an important part in many of the published reports (Table **1**) to demonstrate the safety of the reported compounds.

While the methods used for investigating the toxicity of the compounds varied widely, many of the reported compounds had good safety level (Table **1**).

Several model systems have been used to evaluate the safety of the newly synthesised compounds. Brine shrimp larvae lethality bioassay is commonly reported [77-79] and it has been reported that this method carries several advantages in terms of easiness, cost and time to execute. The cytotoxic activity of the synthesized compounds is measured by determining the IC_{50} (the dose which will kill, or inactivate 50% of the test organism) on brine shrimp at different concentrations. The cytotoxicity of the compounds is evaluated by plotting the percentage of lethality of brine shrimp nauplii versus doses (in ppm) of the examined compounds. IC_{50} is inversely proportional to the toxicity of a compound, i.e. the lower the IC_{50} is, the higher is the activity [77-80]. Another toxicity assay relies on the use of male mice [71-76, 81]. The mice are normally given, either orally and/or through intraperitoneal injection, different concentrations of the tested compounds (in mg/kg animal weight) and the survival of the animals is monitored for up to 7 days of the induction. Other methods used biochemical parameters/ and or histopathological techniques for animal organs [82-84] or cells [66, 84] to examine the safety of the new pyrazole derivatives. Clearly, all these methods differ greatly in terms of sensitivity, the toxicological level of interest and relevance to actual human metabolism. This means that a direct comparison among different compounds and any conclusion relating the structure of the published compounds and their safety level will not be possible. The need to develop a standardised method to measure the cytotoxicological effects of the new compounds would ensure a greater understanding of structure-safety relationship and better level of comparison of new emerging compounds. Furthermore, such assay should be implemented in future investigations of any new compounds since the safety of a compound will dictate any practical applications.

Indeed, the substituted groups and the site of substitution can affect the toxicity of pyrazole derivatives to great extent (Table **1**). The functional group at position-4 on pyrazole ring was reported to dictate the cytotoxic effects of the synthesised compounds [77]. For example, the presence of two bromo groups at position-4 of the pyrazole ring and cyclization of thiosemicarbazone/semicarbazones [77]; acetyl group ($-COCH_3$) [80]; 1,3,4-thiadiazoline [85]; iodo or hydroxyl [84] would increase the cytotoxicity of the derivatives compared with having methylene ($>CH_2$), carbonyl (>C=O), imine (>C=N-) in the same position [80, 84, 85].

SUMMARY AND FUTURE MERIT

We have described the anti-inflammatory and/or antimicrobial activity of several pyrazole analogues, like compounds **26b** and **27,** which exhibited comparable activity to existing drugs. Compound **10** with an alkyl halide substituent had shown promising anti-inflammatory activity and compound **21** exhibited good antibacterial activities. Compound **26** demonstrated promising dual activities. Considering the toxicity of the new compounds entity, further investigations into their detailed mechanism of action are necessary. To this end, pyrazole nucleus can be regarded as one of the most active components present in many standard drugs. Pyrazoles are promising candidates for the future development of novel drugs for the treatments of microbial infection and/or inflammatory diseases.

Table 1. Summary for Cytotoxicity Data of New Pyrazole Compounds

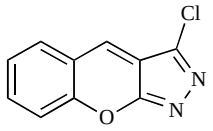
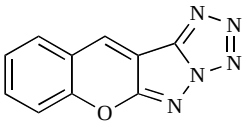
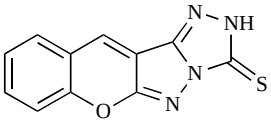
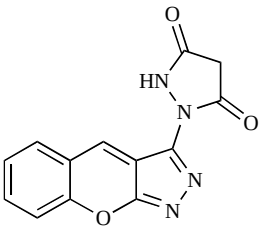
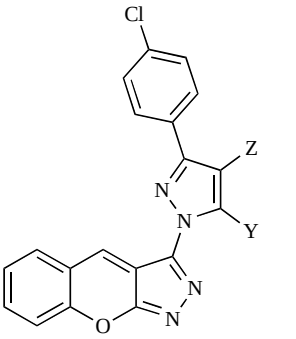
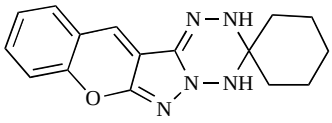
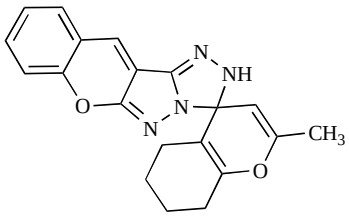
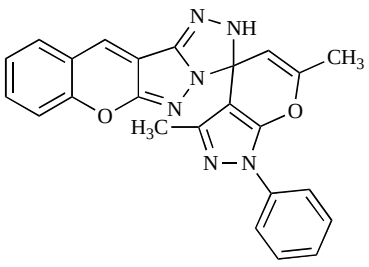
Structure	System used		Cytotoxic Effect	Ref.
	brine shrimp larvae lethality bioassay		Non Toxic	[79]
			Non Toxic	
			Non Toxic	
			Non Toxic	
		Y= CN Z= NH_2	High toxicity	
			Non Toxic	
			Low toxicity	
			Non Toxic	

Table 1. contd….

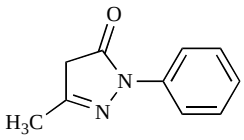
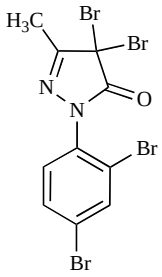
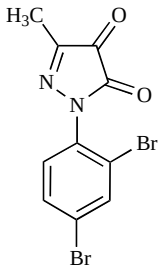
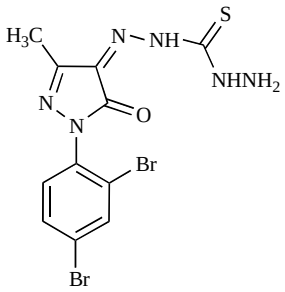
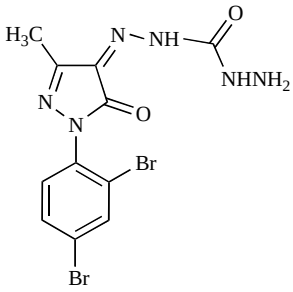
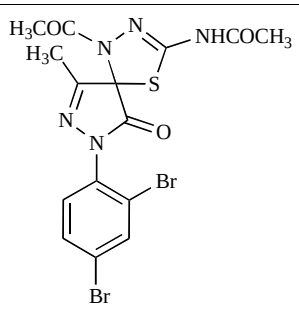
Structure	System used		Cytotoxic Effect	Ref.
	brine shrimp larvae lethality bioassay		Moderately toxic	[77]
			Highly toxic	
			Moderately toxic	
			Moderately toxic	
			Moderately toxic	
			Highly toxic	

Table 1. contd….

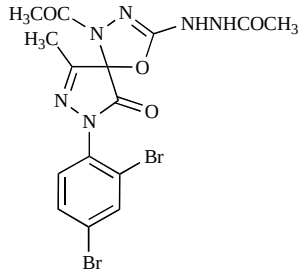
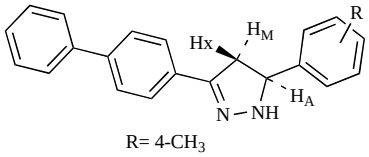
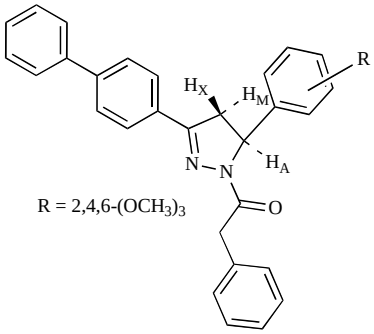
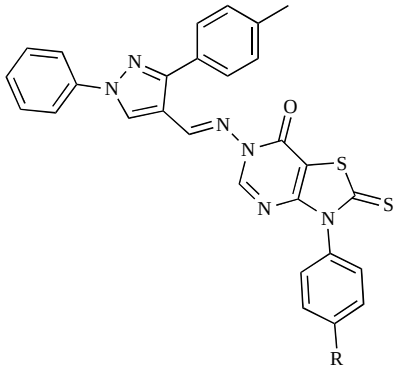
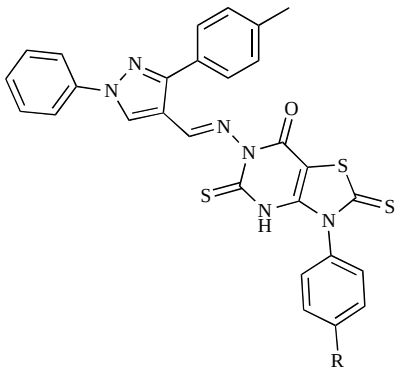
Structure	System used		Cytotoxic Effect	Ref.
			Highly toxic	
 R= 4-CH_3	biochemical parameters (serum enzymes, total protein, and total albumin) and histopathology of liver		The biochemical parameters and the histopatholo-gical studies were not different compared to control	[82]
 R = 2,4,6-$(OCH_3)_3$				
	LD_{50} in male Mice		>250 mg/kg	[70]
			>500 mg/kg	

Table 1. contd….

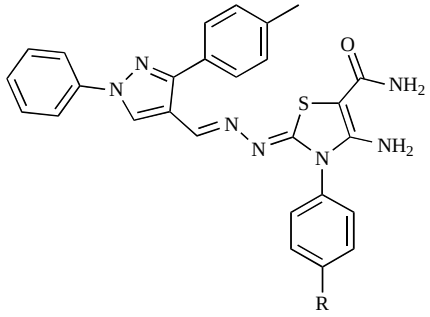
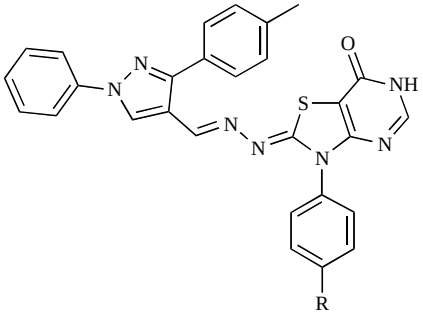
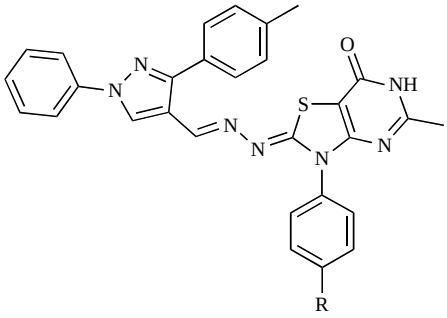
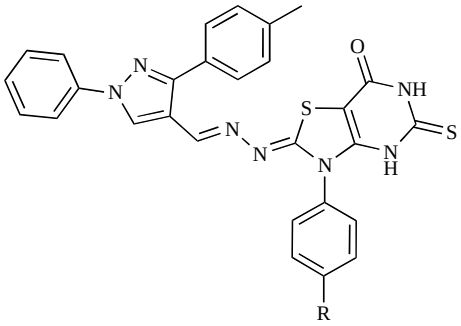
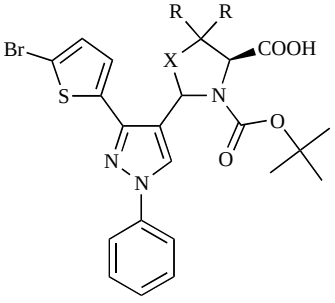
Structure	System used		Cytotoxic Effect	Ref.
				
				
				
				
	LD_{50} in male Mice	R = H, CH_3	>500 mg/kg	[70]

Table 1. contd….

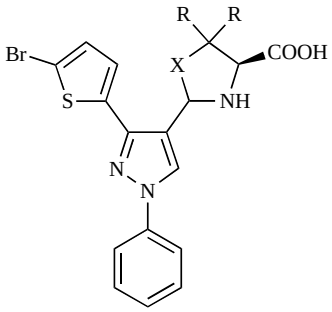
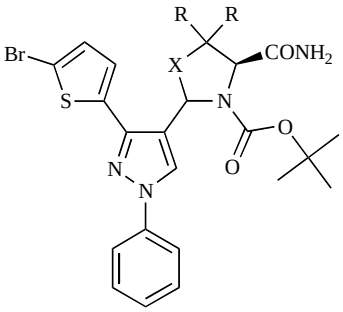
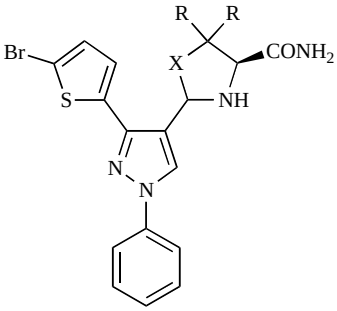
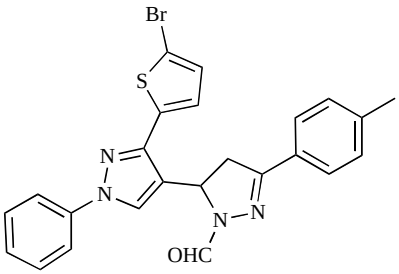
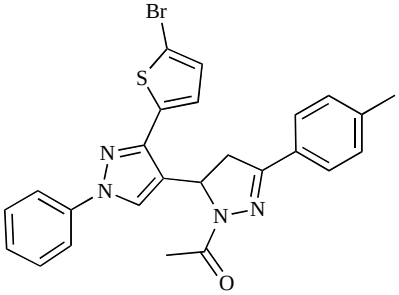
Structure	System used		Cytotoxic Effect	Ref.
		R = H, CH_3		
		R = H, CH_3		
		R = H, CH_3		
	LD_{50} in male Mice		>500 mg/kg	[72]
				

Table 1. contd….

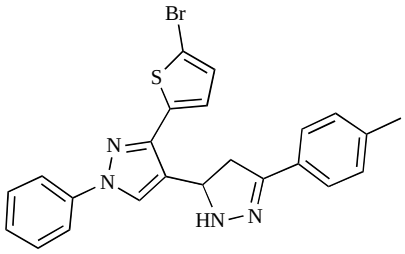
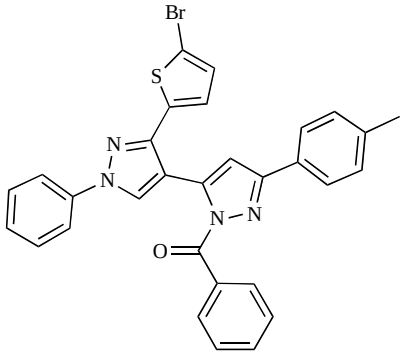
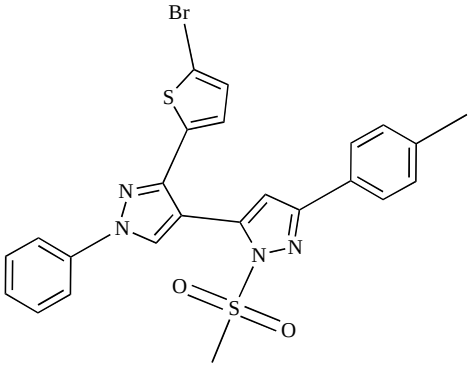
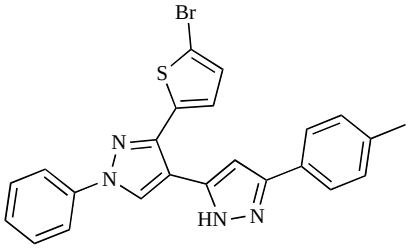
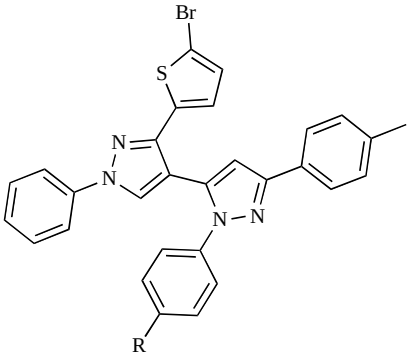
Structure	System used		Cytotoxic Effect	Ref.
				
				
				
				
				

Table 1. contd….

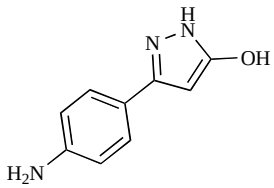
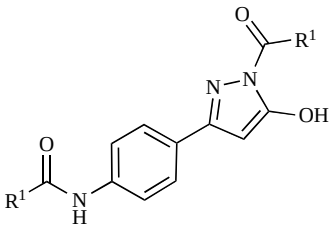
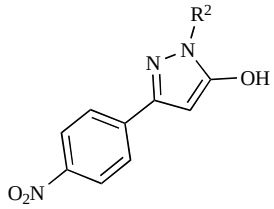
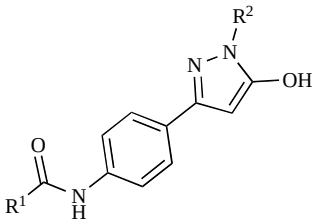
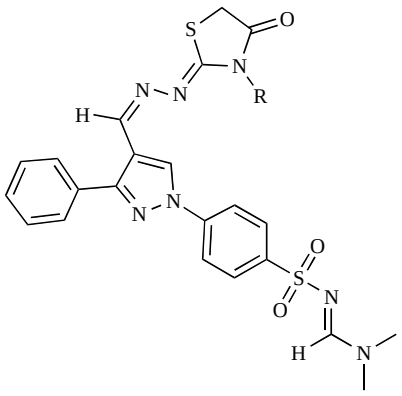
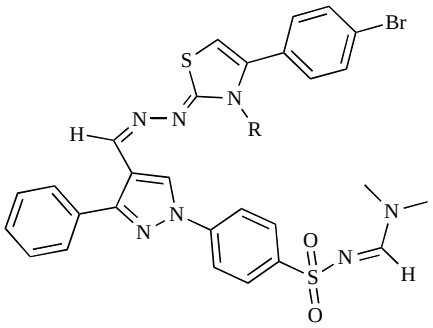
Structure	System used		Cytotoxic Effect	Ref.
	LD_{50} in male Mice		Non toxic up to 120 mg/kg	[75]
				
				
				
	LD_{50} in male Mice	R = 4-$CH_3C_6H_4$ or R = 4-ClC_6H_4	Non-toxic up to 65 mg/kg	Bekhit *et al.* (2008)
		R = 4-$CH_3C_6H_4$		

Table 1. contd….

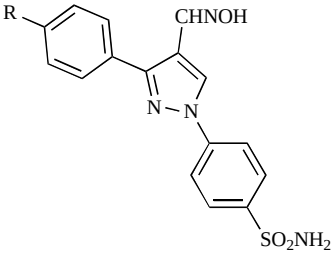
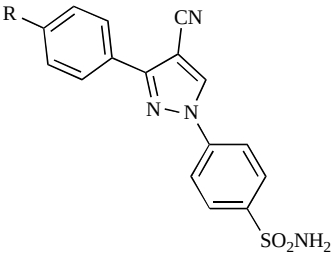
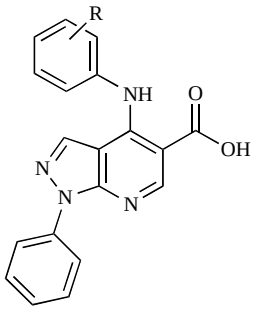
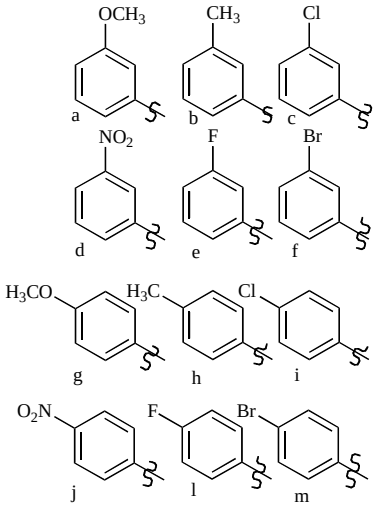
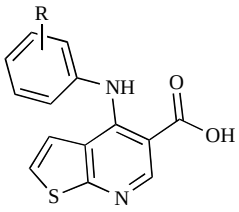
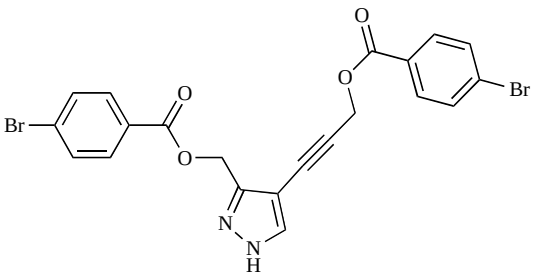
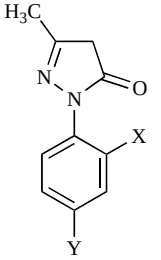
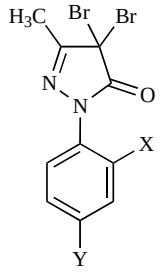
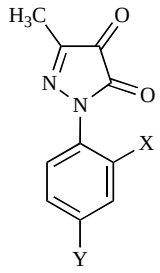
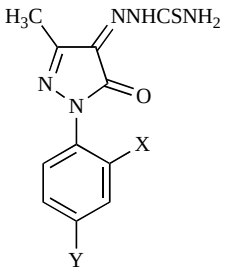
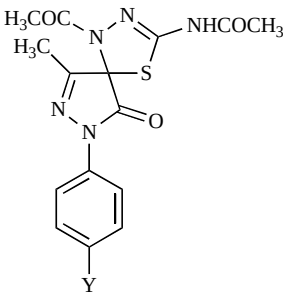
Structure	System used		Cytotoxic Effect	Ref.
	LD_{50} in male Mice	R = H, CH_3, Br, Cl, NO_2	140 mg/kg	[74]
		R = H, CH_3, Br, Cl, NO_2		
	cytotoxicity profile of the compounds, was investigated using peripheral blood mononuclear cells (PBMCs)		All compounds except 1J and 1M demonstrated no toxicity at 700 μM	[66]
				
	Mice		>2500 mg/kg	[81]
	brine shrimp larvae lethality bioassay	X=Y=NO_2	Moderately toxic	Uddin (2000)

Table 1. contd….

Structure	System used		Cytotoxic Effect	Ref.
			Highly toxic	
			Moderately toxic	
			Moderately toxic	
			Highly toxic	

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