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TABLE OF CONTENTS

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ORIGINAL ARTICLE

Identification of the new progress on Pyrazole Derivatives Molecules as Antimicrobial and Antifungal Agents

Identification Des Nouveaux Progrès Sur Les Molécules Dérivées Du Pyrazole Comme Agents Antimicrobiens Et Antifongiques

[1,2]*F. E. Bennani, [3]L. Doudach, [4]Y. El rhayam, [2]K. Karrouchi, [1]Y. Cherrah, [1]A. Tarib,[2,#]M. Ansar, [1,#]M. E. A. Faouzi

ABSTRACT

Microbial infections remain a worldwide leading cause of death, despite the evolution of a large number of new antibiotics every year. Currently, several bacteria have developed resistance against antibiotics drugs which remain a major issue in antibiotics drug discovery. This review provides detailed information about antimicrobial and antifungal agent synthesis belonging to the pyrazoles scaffold. We reassemble the results obtained from several studies to characterize the importance of heteroatom nuclei in many synthetic products. Additionally, several compounds based on pyrazole derivatives such as benzimidazole, benzothiazole, indole, acridine, oxadiazole, imidazole, isoxazole, pyrazole, triazole, quinoline and quinazoline including other pyrazole containing drugs such as pyridazine, pyridine and pyrimidine are highlighted. Furthermore, you will find in this review 134 best promise structures collected from recent studies, relating the pyrazoles structures to the relevant biological activities, in particular, antimicrobial and antifungal one. **WAJM 2022; 39(11): 1217–1244.**

Keywords: Pyrazoles derivatives; antibiotics; antifungal activity; microbial resistance, heterocyclic nitrogen.

RÉSUMÉ

Les infections microbiennes restent une des principales causes de décès dans le monde, malgré l'évolution d'un grand nombre de nouveaux antibiotiques chaque année. Actuellement, plusieurs bactéries ont développé une résistance aux médicaments antibiotiques, ce qui reste un problème majeur dans la découverte de médicaments antibiotiques. Cette revue fournit des informations détaillées sur la synthèse d'agents antimicrobiens et antifongiques appartenant à l'échafaudage des pyrazoles. Nous rassemblons les résultats obtenus à partir de plusieurs études pour caractériser l'importance des noyaux d'hétéroatomes dans de nombreux produits synthétiques. En outre, plusieurs composés basés sur des dérivés du pyrazole tels que le benzimidazole, le benzothiazole, l'indole, l'acridine, l'oxadiazole, l'imidazole, l'isoxazole, le pyrazole, le triazole, la quinoléine et la quinazoline, ainsi que d'autres médicaments contenant du pyrazole comme la pyridazine, la pyridine et la pyrimidine, sont mis en évidence. En outre, vous trouverez dans cette revue 134 structures les plus prometteuses recueillies dans des études récentes, mettant en relation les structures des pyrazoles avec les activités biologiques pertinentes, en particulier antimicrobiennes et antifongiques. **WAJM 2022; 39(11): 1217–1244.**

Mots-clés: Dérivés de pyrazoles ; antibiotiques ; activité antifongique; résistance microbienne, azote hétérocyclique.

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INTRODUCTION

When an antibiotic has been used several times improperly in the treatment of microbial infections, it allows the bacteria to develop resistance[1] such that we are faced with one or more micro-organisms that are highly drug-resistant to the treatment administered. In this regard, society is confronted with "the main dangerous threat to health which is resistance to antibiotics.[1] Due to the lifting of the antibacterial opposition, 0.01 billion lives a year and a cumulative budget production of 100,000 billion US dollars of antibiotics will be in danger by 2050.[2] In these microbial resistance difficulties, Gram-negative bacteria are mainly troublesome because they become more and more resistant to almost all drugs.[1] This comes back to the nature of the membrane which behaves as a barrier made up of various elements, notably antibacterial drugs.[3,4]

In the light of the above, the discovery and synthesis of new anti-biotic structures, adjuvants to antibiotics and anti-fungal distinct from those which currently exist and thus controlling resistance is necessary.[5,6]

The design and development of a synthetic approach for the conversion of a conductive molecule into bioactive heterocycles is one of the attractive participation in biochemistry. Today, antibiotic compounds derived from natural resources are used in the care and the fight against bacteria, and it has become an integral part of today's health system, which is helping the natural immune system fight pathogens. The medical authority has announced that it faces serious problems with antibiotic resistance, which has led the World Health Organisation (WHO) to classify this type of resistance among the serious threats that are no longer expected in the future, let alone at the present. In all regions of the world, it is likely to affect anyone, any age, and any country. The first report issued on April 30, 2014, by the World Health Organisation revealed the potential of antibiotics to create a global threat to the public health of humanity. It was accessed on December 21 of the same year. This made these new mutations gain immunity against old treatments as well as against the development of new effective antibiotics that are alternatives to the old antibacterial treatments.[7,8]

Among known chemical compounds, heterocyclic compounds constitute an important class, which is an essential part of all the most common organic compounds. These heterocyclic complexes also have a range of physical, chemical and biological properties which make them of interest to many researchers.[9] In recent years, heterocyclic nitrogen compounds such as pyridine, pyrazole and piperidine have been widely recognized by researchers and specialists in view of high biological activity in several fields: Anti-microbial, anti-fungal, anti-inflammatory, anti-cancer etc.[10] These types of compounds and their families are an important resource in medicinal chemistry as they represent an interesting class of nitrogen compounds.[11]

Pyrazole and their families are considered an essential asset in drug chemistry. This comes down to the intrinsic properties it contains, which explains a wide field of application. These special properties of pyrazole have contributed to many important therapeutic productions, especially in the field of pharmaceutical chemistry.[12,13] We mention, for example, the contribution against cancer.[14,15] In addition, a bibliographic study proved that the benzofuran and pyrazole fractions had various pharmacological activities, mainly anti-tumor.[16,17]

The present review focuses on the antibiotics and antifungals drug classes of pyrazole-base and reports the best structures of recently carried out pyrazole derivatives as potential new and effective treatments against microbial infections.

Results based on the literature

Below, we present the main results obtained from the literature, regarding the new progress of pyrazole and its derivation as a biological agent against bacteria and fungi. Note that all[13] C NMR and Mass spectrums are summarized in supplementary data.

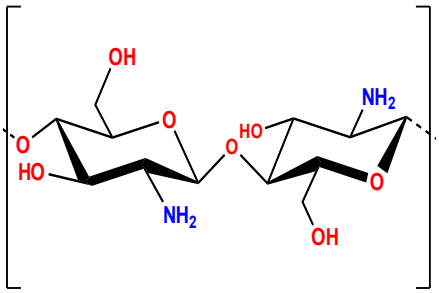


Fig. 1: Chemical Structure of Chitosan

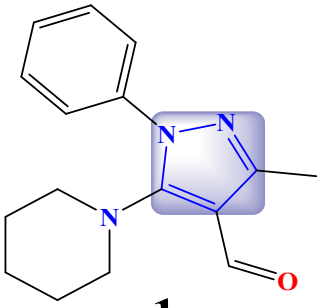
1. Reaction of Chitosan with different substituted pyrazole-4-carbaldehydes

Chitosan, the linear polymer, is produced by alkaline deacetylation of chitin (CHI). Recently, chitin and chitosan have established themselves among the other compounds (Figure 1) among chemists and biologists for their biocompatibility, biodegradability, and nontoxicity. This raw material is demineralized by hydrochloric acid treatment, then deproteinized with caustic soda or potassium and finally discolored using an oxidizing agent.

Anush, *et al*[18] have synthesized a series of Chitosan Schiff bases CSSB prepared with different pyrazole derivatives. These products have been identified with different analysis methods. This synthesis aims to discover new

Table 1: The Antibacterial, Anti-fungal Activity of CS Derivatives (Chitosan) and CSSB (Chitosan Schiff Bases)

Compounds	Gram-positive Bacteria MIC (μgmL^{-1})		Gram-negative Bacteria MIC (μgmL^{-1})		Champignon MIC (μgmL^{-1})
	S. aureus	*B. subtilis*	*K. pneumoniae*	*E. coli*	*C. albicans*
(1)	100	100	100	100	100
(2)	12.5	6.25	25	6.25	12.5
(3)	25	12.5	50	12.25	25
(4)	25	25	50	25	25
(5)	50	50	50	50	50
CS-piperidin	25	12.5	50	50	50



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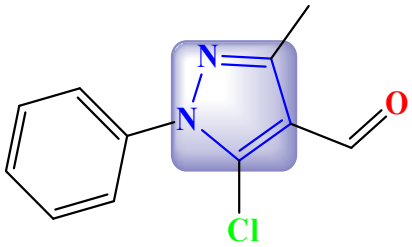
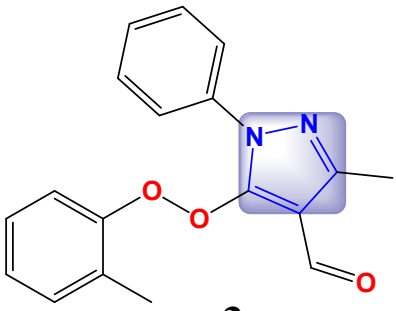
3-methyl-1-phenyl-5-(piperidin-1-yl)-1 *H*-pyrazole-4-carbaldehyde



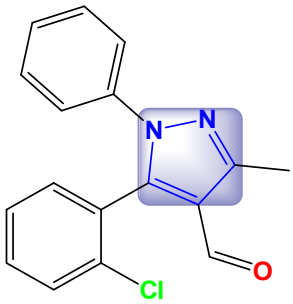
2

5-chloro-3-methyl-1-phenyl-1 *H*-pyrazole-4-carbaldehyde



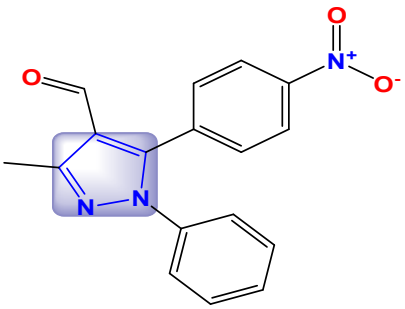
3

3-methyl-1-phenyl-5-(*o*-tolylperoxy)-1 *H*-pyrazole-4-carbaldehyde



4

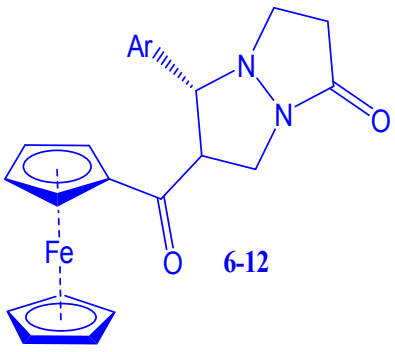
5-(2-chlorophenyl)-3-methyl-1-phenyl-1 *H*-pyrazole-4-carbaldehyde



5

3-methyl-5-(4-nitrophenyl)-1-phenyl-1 *H*-pyrazole-4-carbaldehyde

Fig. 2: Structures of an Analogue of CS and CSSB Derivatives against Blue-Colored Bacteria and Red-Colored Bacteria



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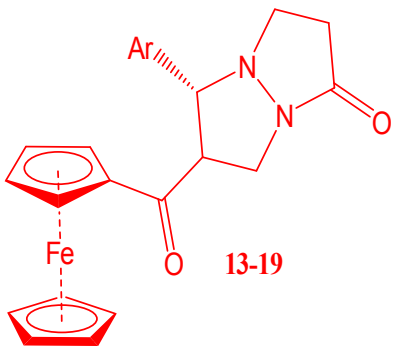


13-19

Fig. 3: Structures of Tetrahydro Pyrazole Pyrazolones Derivatives Containing Ferrocene

candidate molecules intended against bacteria and fungi. This team carried out an antimicrobial test based on a staining technique based on the membrane characteristics of bacteria. In this work, the blue-colored bacteria (Gram-positive) are: Staphylococcus aureus, Bacillus subtilis; and the bacteria which are characterized by red (Gram-negative) colors are: *Klebsiella pneumoniae*, Escherichia coli and the fungus Candida albicans.

The authors tried to modify Chitosan with the pyrazole carbaldehyde fragment to obtain a better antimicrobial activity. The set of the modified pyrazole carbaldehyde derivative is illustrated below (Figure 2).

The results obtained were compared with those of Chitosan and illustrated in Table 1.

The results obtained show that the inhibitor effects of Chitosan Schiff bases are always higher than those of compound 1. The table also shows that this compound was more effective at higher concentrations of 100 µg/mL, while Chitosan Schiff bases showed an inhibitory effect at low concentrations of 6 to 50 µg/mL against the tested bacteria. They also report that the inhibitory effect of Chitosan Schiff bases compounds against blue colored bacteria and red colored bacteria was classified as follows: 2> 4> 3 = CS-piperidine>5. Compound 2 at maximum inhibitory capacity among these compounds was a MIC value of 6.25 µg / ml. In this context, to clarify their interactions between these derivatives and the studied bacteria, several mechanisms were reported on the Chitosan antimicrobial activity, including three mechanisms which are the more accepted ones.

The first concerns the electrostatic interactions created by the positively-charged amines of chitosan as well as the negatively-charged surface of the microbial cell[19] which is responsible of the antimicrobial property. This anti-microbial property is mainly regulated by the substitution degree, the grafted chain nature (donors / acceptors), and the derivative hydrophobicity.

The second mechanism considers Chitosan binding to microbial DNA that inhibits the composition of mRNA and

proteins by Chitosan penetration into the microorganism nucleus.[20]

Third mechanism considers Chitosan chelation with metals, resulting in the suppression of spores and essential nutrients binding to stop microbial growth.[21]

2. Tetrahydropyrazolopyrazolones containing ferrocene

Organometallic complexes have specific physicochemical properties. Among the properties exploited for the creation of compounds with biological activities, one can cite: their structural diversity, the possibility of exchange of their ligands, their catalytic properties and their redox properties.

Bugarinović, *et al*[22] designed a family based on pyrazolopyrazolones containing ferrocene, these molecules have been evaluated against red- and blue-colored bacteria. The results obtained are shown in Table 2.

Compound 9 shows a better effect on blue-colored bacteria having MIC values <0.02 and 0.28 mM against *E. coli* and *S. enteritidis* respectively. Also, the maximum concentration of the isomer inhibitor 13 were less than 0.28 mM with respect to the same bacteria based on the membrane staining. The other molecules designed were less active towards these two bacterial types having MIC values greater than 2 mM. *S. enteritidis* was the most resistant bacterium, while the ferrocenyl derivatives were the most effective against *B. cereus* with the lowest MIC value (0.06 mM) 6.

It is evident that there is no considerable difference between the MIC values of the ferrocinil families associated with bacteria or fungi, as it is observed that the fungal strains are more sensational than the bacterial strains. The antifungal effects of the combined molecules are expressed in MIC (mm) against the three selected molds and C. albicans shown in Table 3.

According to the results obtained (Table 3), the authors reported that nearly the majority of the molecules examined had MICs included in the concentration scale examined for all the fungal classes examined; therefore, they reported that compound 21 is the most promising compared to *C. albicans* at a MIC value of less than 0.02 mM, while the lowest MICs (0.13 mM) of *A. Brasiliensis* were obtained for the two 1-naphthyl isomers 11 and 16. They added that *A. brasiliensis* was less sensational to the molecules examined than the other selected fungus, which was not very far from half of the compounds examined and had no influence on its growth at all the concentrations performed.

Then, compound 20 exhibits the highest antifungal effect compared to *F. oxysporum* at a MIC of 0.29 mM, considering that *P. canescens* was the most sensational at molecule 16, at a MIC value around 0 , 27 mM (Figure 3). Molecules 20 and 22 were less active against *P. canescens,* at similar MIC values (0.56 and 0.59 mM), although the MICs of the other molecules examined were greater than 1 for this set. All of the compounds designed have shown better antimicrobial properties than Molecule 19.

The molecule 18 was more powerful versus fungal type than the other designed molecules.

3-Hydrazone (1-benzylidene-2-(2,5-dimethyl-phenyl) -hydrazine)

To find a more biological active molecule against bacteria, Çetin and Bildirici[23] have developed a novel family of pyrazole founded on pyrazolo-pyridazine. The antibacterial effect of the new structures was tested *in vitro* and defined in relation to bacteria of blue colors, in particular Bacillus subtilius, Staphylococcus aureus, and bacteria of red colors, as *Escherichia coli, Pseudomonas aeroginosa* and *Klebsiella pneumonia,* the results obtained by this team are illustrated in the Table below (Table 4).

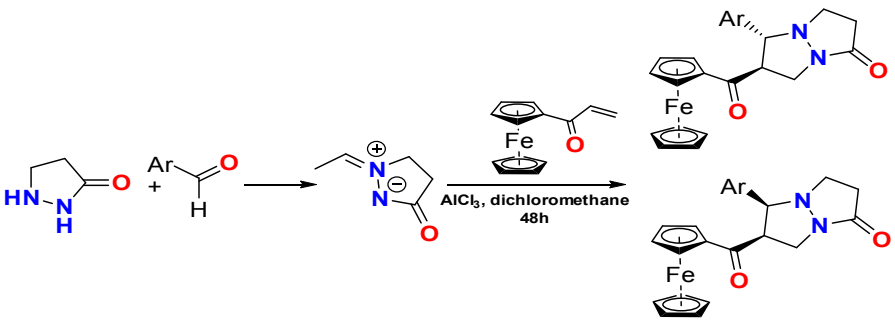
Some of the molecules designed showed minimal inhibitory concentrations (MIC, µg/ml) and the zone of inhibition (mm) in relation to all blue- and red-colored bacteria are selected. The obtained results (Table 4) show that some synthesized compounds, especially 23, 24, 26, 27, 28, 29, 30, 31, 32, 33, and 34 (Figure 4) have shown an activity superior to that of amikacin against S aureus (MIC, 25–100 µg / mL). Compounds 23, 27, 28, 29, 30, 33, and 34 (Figure 4) have shown elevated antimicrobial effect than rifampicin versus *P. aeroginosa* strain.

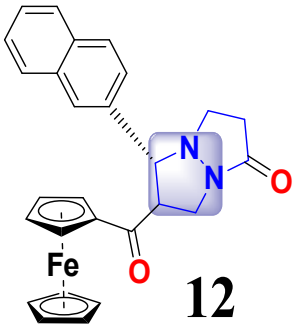
The authors, likewise, denounce that the compounds 23 and 31 showed higher inhibitory activities than amikacin against *K. Pneumonia,* (MIC 100 µg/mL) among all the tested compounds. However, the compounds 23, 24, 29 and 30 have shown more inhibitory activities than amikacin versus *B. subtilius*.

The authors have concluded that the new designed molecules could have

Table 2: Antibacterial activity of newly Synthesized Products (6–19)

Compounds	Aryl Substitution/Ar 6–12 and 13–19	Gram-negative Bacteria		Gram-positive Bacteria	
		E. coli	*S. enteritidis*	*B. cereus*	*S. aureus*
		MIC (mM)			
(6)	2,4,6-MePh	>2.19	>2.19	0.06	>2.19
(7)	2-MeOPh	>2.25	>2.25	>2.25	>2.25
(8)	3-MeOPh	>2.25	>2.25	>2.25	>2.25
(9)	4-MeOPh	<0.02	0.28	0.56	1.12
(10)	4-NO_2Ph	>2.18	>2.18	>2.18	>2.18
(11)	1-Naph	>2.15	>2.15	>2.15	>2.15
(12)	2-Naph	>2.15	>2.15	>2.15	>2.15
(13)	4-MeOPh	0.28	0.28	1.12	2.25
(14)	3-MeOPh	>2.25	>2.25	0.28	>2.25
(15)	4-NO_2Ph	>2.18	>2.18	>2.18	>2.18
(16)	1-Naph	>2.15	>2.15	0.27	>2.15
(17)	2-Naph	>2.15	>2.15	>2.15	>2.15
(18)	–	4.17	4.17	0.07	4.17
(19)	–	>11.49	>11.49	>11.49	>11.49
Erythromycin	–	0.0272	0.0545	<0.0004	<0.0004
Ciprofloxacin	–	<0.0009	<0.0009	<0.0009	<0.0009





12

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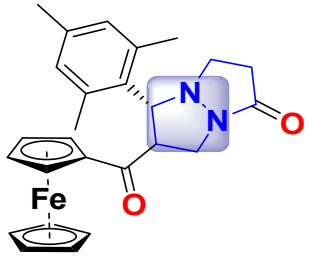

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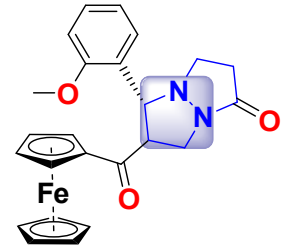

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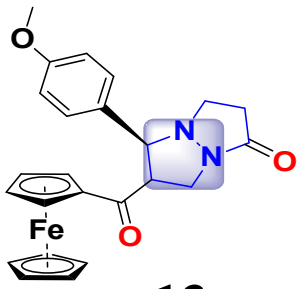

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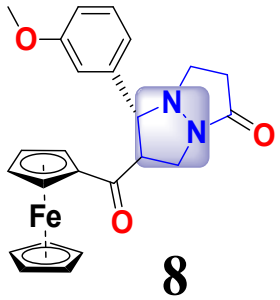

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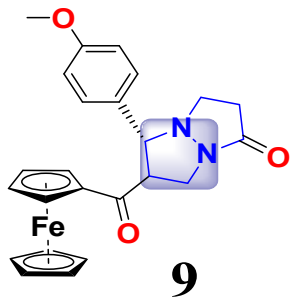

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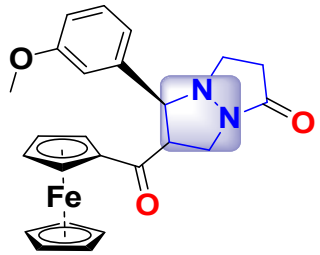

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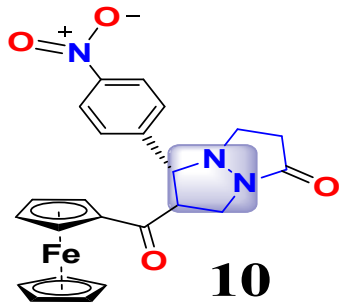

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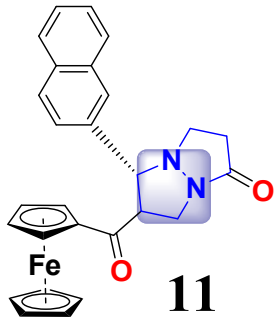

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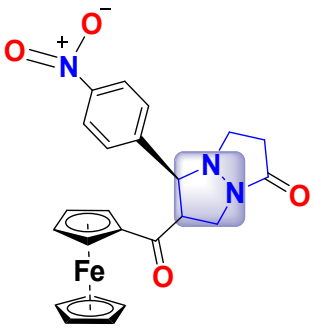
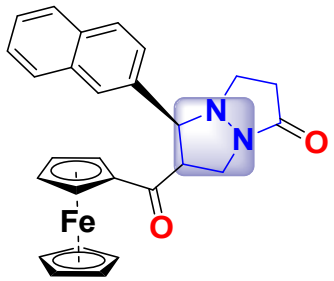


15

cis-6-ferrocenoyl-5-(4-nitrophenyl) tetrahydropyrazolo[1,2-a]pyrazol-1(5H)-one

a likely antibacterial effect due to the presence of pyrazole, pyridazine, oxazine, and pyrrole cycles. In addition to these pyrazole-based sets, some synthesized compounds containing chlorine and fluorinated groups situated at different positions of the phenyl nucleus have shown similar activities to those of the origine drugs. The molecule containing electron-attracting groups situated at



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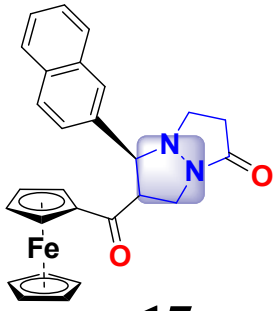

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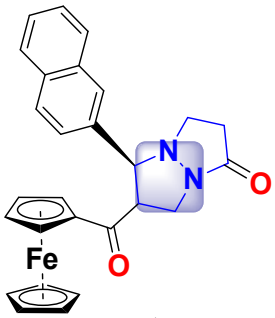

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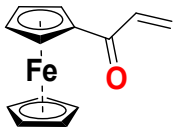
cis-6-ferrocenoyl-5-(naphthalen-2-yl) tetrahydropyrazolo[1,2-a]pyrazol-1(5H)-one



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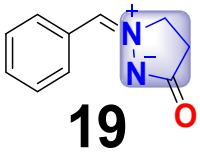

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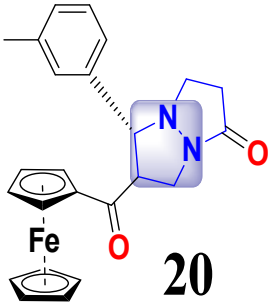
(Z)-2-benzylidene-5-oxopyrazolidin-2-ium-1-ide



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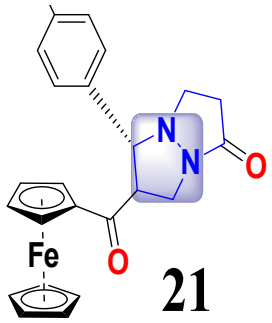
trans-6-ferrocenoyl-5-(3-methylphenyl) tetrahydropyrazolo[1,2-a]pyrazol-1(5H)-ones



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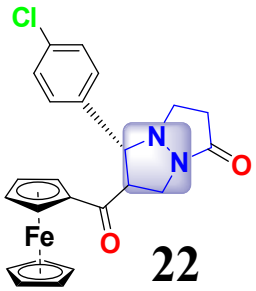
trans-6-ferrocenoyl-5-(4-methylphenyl) tetrahydropyrazolo[1,2-a]pyrazol-1(5H)-ones



22

trans-6-ferrocenoyl-5-(4-chlorophenyl) tetrahydropyrazolo[1,2-a]pyrazol-1(5H)-ones

Fig. 3: Structures of synthesized Pyrazole Ferrocenyl Derivatives with Antibacterial Activity.

another positions, such as chlorine and fluorine, have shown agreeable effect versus *P. aeroginisa* and *S. aureus*.

The results reveal that the substituents with another groups such as chlorine, fluorine, methyl and nitro are capable of increasing the biological activity of the synthesized moleculs.

4-Pyranopyrazole Nanocomposite

Another recent work reported by Shahbazi and col,[24] highlighting a new set of pyrazole synthesis based on pyranopyrazole nanostructures of coated cobalt oxide with silca amino functionalized as catalyst. To study the antibacterial and antifungal activities of the pyranopyrazoles nanocomposite, they chose a blue-colored bacterium, which is *S. aureus* (resistance to methicillin) and the other red-colored bacterium which are *E. coli, P. aeruginosa.* For antifungal activity, they chose *C. albicans,* then, they measured the MIC. The result of minimum concentration of inhibition (MIC) is summarized in Table 5. It showed that the synthesized derivatives (4-Br), (4-F) and (2; 4-Cl) bromobenzaldehyde had the greatest impact on *S. aureus* (Table 5).

According to the antimicrobial test results by diffusion on disc, three compounds among the heterocycles synthesized which are substituted by the electron-withdrawing groups (4-Br), (4-F) and (2; 4-Cl), had an antimicrobial activity on *S. aureus* and no significant effect was recorded against Gram-negative bacteria and fungus.

According to this study and due to the size of the diagonals, the absence of bacterial growth was observed in various associations combining a compound substituted by Br from two other diagonals, the lack of growth being greater for a size of 17 mm.. Two other combinations of MICs, equal to 50 at higher concentrations, prevent the growth of bacteria. According to the results of specified antimicrobial tests, the active antibacterial compound of 4-Br is more robust than other two-component compounds.

5. Pyrazole Ester Derivatives

In order to design a new family of pyrazole ester, containing the triazole

Table 3: Antifungal Effects of Synthesized Compounds

Compounds	*C. albicans*	*A. brasiliensis*	*P. canescens*	*F. oxysporum*
	MIC (mM)			
(20)	0.58	>2.34	0.58	0.29
(21)	<0.02	>2.34	>2.34	0.58
(11)	2.15	0.13	1.07	2.15
(16)	1.07	0.13	0.27	1.07
(22)	0.14	>2.23	0.56	0.56
(18)	0.13	1.04	0.52	0.52
(19)	11.49	5.74	5.74	5.74
Nystatin	0.0027	0.0054	<0.0003	0.0003
Ketoconazole	0.0753	0.0753	<0.0005	0.0005

Table 4: Minimal inhibitory Concentrations (MIC, µg/ml) and Inhibition Zone (mm) of some Novel Synthesized Molecules (23–34)

Compounds	MIC in µg/mL and Zone of Inhibition (mm) Bacteria				
	Gram-positive Bacteria		Gram-negative Bacteria		
	B. subtilis	*S. aureus*	*E. coli*	*P. aeroginosa*	*K. pneumonia*
(23)	50(12)	100(11)	50(10)	25(10)	100(11)
(24)	50(13)	100(10)	100(10)	–	50(10)
(25)	100(12)	50(10)	50(10)	–	50(10)
(26)	100(10)	100(10)	50(9)	–	50(9)
(27)	50(11)	100(10)	100(10)	–	50(9)
(28)	50(10)	50(10)	50(9)	50(10)	50(9)
(29)	25(13)	50(13)	50(12)	50(10)	100(10)
(30)	25(13)	50(12)	50(11)	100(9)	50(9)
(31)	50(11)	100(11)	50(11)	100(10)	100(11)
(32)	100(9)	50(10)	–	–	100(9)
(33)	100(11)	50(10)	50(11)	50(10)	50(9)
(34)	100(11)	100(10)	50(11)	100(10)	50(9)
Erythromycin	100(20)	100(21)	100(19)	100 (19)	100 (19)
Rifampicin	100(21)	100 (18)	100 (18)	100 (8)	100 (19)
Amikacin	100 (11)	100 (9)	100 (13)	100 (14)	100 (10)

[a]*MIC: Minimal inhibitory concentration values with SEM= 0,02.*
[b]*(-): Totally inactive (no inhibition)*

have been synthesized and characterized by Chu, *et al.*[25] Their biological activities have been studied versus blue colored bacteria (*S. aureus* , *L. monocytogenes*) and red colored bacteria, (*E. coli*, *S. gallinarum*) by using diffusion and minimal inhibition method.

Antimicrobial activity was effected in vitro of pyrazole ester molecules opposed to four bacteria. This has been evaluated by the classical method of dilution in agar with, as a reference, the ciprofloxacin. The obtained results are illustrated in Table 6.

As indicated in Table 6, the molecule 38 (Figure 6) presents the most powerful antibacterial activity among the intermediate compounds a MIC of 16 µg/ml; however, among the target molecules examined, two of them: 40 and 43 (Figure 6) exhibited the most potent effect around: 4, 2, 4 and 0.5 gµ/ml, and 4, 8, 4 and 4 gµ / ml, relative to *S. aureus, L. monocytogenes, E. coli* and *S. gallinarum,* similar to the wide range antibiotic ciprofloxacin.

The compound 39 (Figure 6) showed antibacterial activities against *S. aureus*, *L. monocytogenes*, *E. coli*, and *S. gallinarum*. Then, the authors introduced different groups on the benzene cycle compound 39. The incorporation of the methyl in group R^1 had meaningfully improved effects in comparaison to the effects of other compounds.

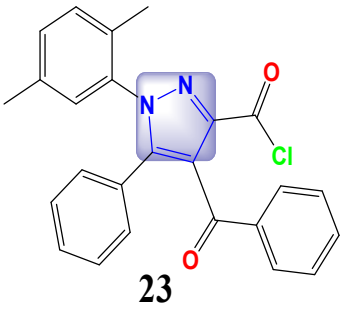
The compound 40 (Figure 6) presented the best antibacterial activity compared to the others. The authors concluded that when the position R^2 was replaced by fluorine, the substituted methyl at the site R^1 was benefecial for the antibacterial activity, for example, compound 42 (Figure 6).

When the R^1 position was substituted by a methyl, the substituents donors of electrons, for example, compounds 43 (Figure 6). in R^1, presented more powerful activities than those with electron-withdrawing, for example, in compounds 44 and 45 (Figure 6).

6. Pyrazolo [1,5-a] Pyrimidine Derivatives

A new series synthesized base of pyrazolo pyrimidine by Fouda, *et al*[26] then evaluated for its antimicrobial activity as opposed to six bacteria stumps. The first group of bacteria is based on the color blue, *(Staphylococcus aureus, Bacillus subtilis,* and *mutant Staphylococcus)* as well as the other based on the color red *(Enterococcus faecalis, Proteus vulgaris* and *Escherichia coli),* while using the Gentamycin (5 mg/ml) as a reference. Futhermore, its antifungal activity has been estimated, versus three fungal stumps *(Aspergillus fumigates, Aspergillus flavus,* and *Candida albicans)* in order to identify the inhibition's zone while using the Ketoconazole (5 mg/ml) as an antifungal standard. The antibacterial activity was assessed measuring the diameter of the inhibition zone in mm as.[27,28] The results obtained are presented in Table 7.

From Table 7, the author noticed that compounds 46, 47 and 53 (Figure 7) exhibited significant and more potent activity compared to *E. faecalis* and *P. vulgaris,* tested for a zone diameter of inhibition around 25 and 40 mm. In addition, compound 46 (Figure 7) showed high antibacterial activity on B. Subtilis for an inhibition zone diameter of 40 mm. The other compound had moderate anti-bacterial activity on other strains with a zone of inhibition from 13 to 25 millimeters.



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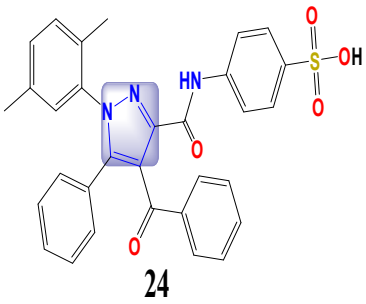
4-benzoyl-1-(2,5-dimethylphenyl)-5-phenyl-1*H*-pyrazole-3-carbonyl chloride



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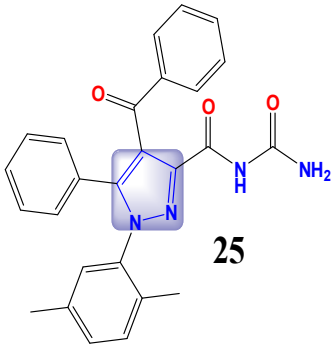
4-(4-benzoyl-1-(2,5-dimethylphenyl)-5-phenyl-1*H*-pyrazole-3-carboxamido)benzenesulfonic acid



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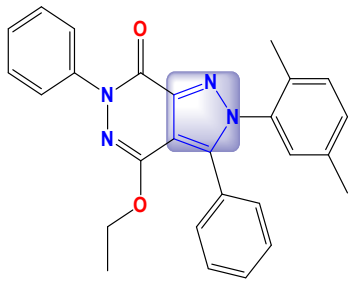
4-benzoyl-*N*-carbamoyl-1-(2,5-dimethylphenyl)-5-phenyl-1*H*-pyrazole-3-carboxamide



28

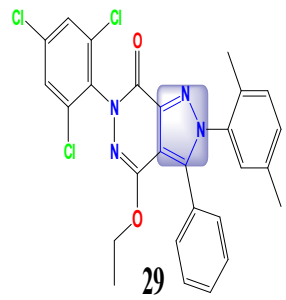
2-(2,5-dimethylphenyl)-4-ethoxy-3,6-diphenyl-2,6-dihydro-7*H*-pyrazolo[3,4-*d*]pyridazin-7-one

Additionally, Molecule 46 exhibited an average antifungal effect as opposed to other fungal strains. Molecule 53 (Figure. 7) exhibited a moderate effect for the other fungal strains, and then molecule 47 was inactive on the fungal strains studied. Then, molecule 48 (Figure 7) gave an acceptable effect on bacterial strains indicating a zone of inhibition ranging from 20 to 24 mm in diameter, thus fungal strains indicating an inhibitory region around 13 to 20 mm.

In addition, molecules 49, 50, 51 and 52 (Figure 7) showed a reasonable effect on the bacterial strains of blue and red color, tested with an inhibition zone between 9 to 18 mm, with the exception of the molecule 49 which was N/A for mutant Streptococcus, whereas the molecules 49, 51 and 52 had no antifungal effect unlike the three fungal strains.

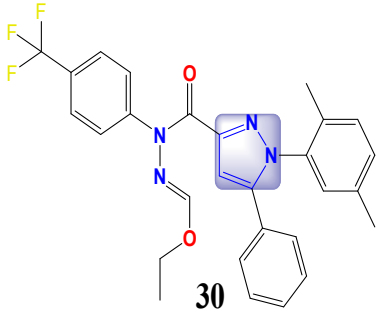
7. Pyrazole Cappeds 2-Azitidinone Derivatives

Bhatt *et al*[29] synthesized new components based on pyrazole capped



29

2-(2,5-dimethylphenyl)-4-ethoxy-3-phenyl-6-(2,4,6-trichlorophenyl)-2,6-dihydro-7*H*-pyrazolo[3,4-*d*]pyridazin-7-one



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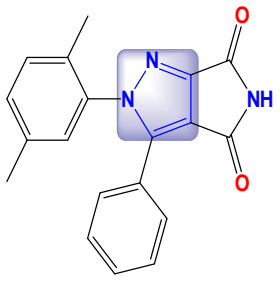
ethyl (E)-N-(1-(2,5-dimethylphenyl)-5-phenyl-1H-pyrazole-3-carbonyl)-N-(4-(trifluoromethyl)phenyl)formohydrazonate



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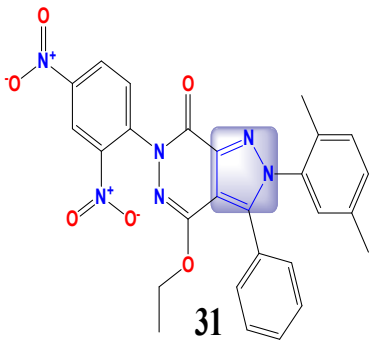
2-(2,5-dimethylphenyl)-3-phenylpyrrolo[3,4-*c*]pyrazole-4,6(2*H*,5*H*)-dione



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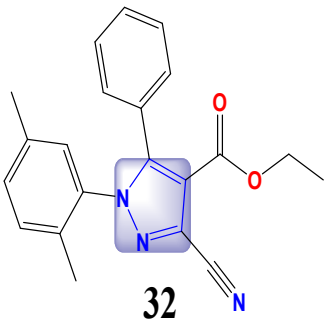
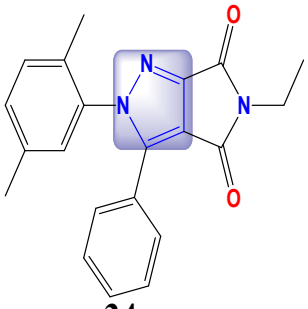
2-(2,5-dimethylphenyl)-6-(2,4-dinitrophenyl)-4-ethoxy-3-phenyl-2,6-dihydro-7*H*-pyrazolo[3,4-*d*]pyridazin-7-one



32

ethyl 3-cyano-1-(2,5-dimethylphenyl)-5-phenyl-1*H*-pyrazole-4-carboxylate



34

2-(2,5-dimethylphenyl)-5-ethyl-3-phenylpyrrolo[3,4-*c*]pyrazole-4,6(2*H*,5*H*)-dione

Fig. 4: Hydrazone Derivative Structures (1-benzylidene-2- (2,5-dimethyl-phenyl) -hydrazine) against Gram Positive and Gram-Negative Bacteria.

Table 5: Anti-bacterial Activity of Compounds (35-37) against *S. aureus* Strain (ATCC 25923)

Compounds No.	Ar	*S. aureus* MIC (mg/mL)
(35)	4–Br	25
(36)	4–F	50
(37)	2,4–Cl	50

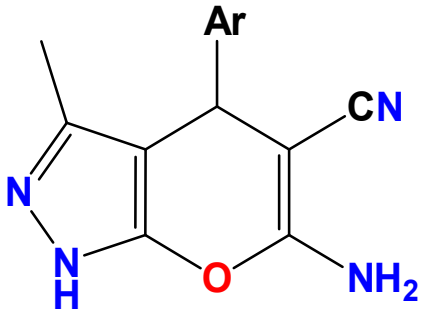
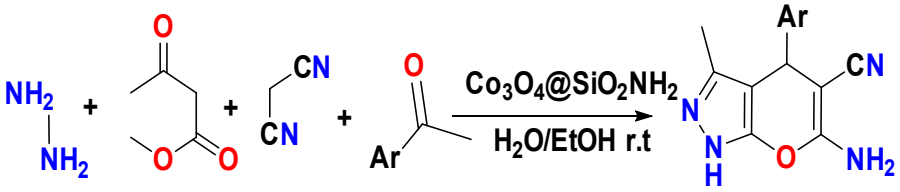
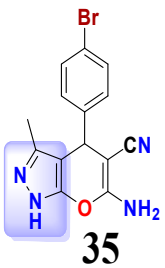


Fig. 5: Co_3O_4@SiO_2 –NH_2 Nano-composites Based on Pyranopyrazoles.

2-Azetidinone. Then, the antimicrobial activities have been studied using a controlled stallion: 19±0,28 and 17,5±0,58 against, respectively, the bacterial stumps Gram-positive as well as Gram-negative. The results obtained are illustrated in Table 8.

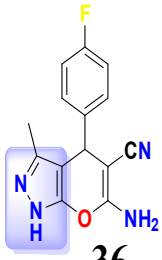
According to Table 8, we noticed that the compound 54 (Figure 8) showed an important antibacterial activity, while the compounds 55 and 56 (Figure 8) presented a moderated activity. The





35

6-amino-4-(4-bromophenyl)-3-methyl-1,4-dihydropyrano[2,3-c]pyrazole-5-carbonitrile



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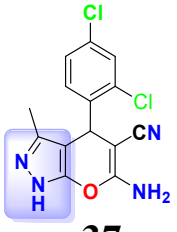
6-amino-4-(4-fluorophenyl)-3-methyl-1,4-dihydropyrano[2,3-c]pyrazole-5-carbonitrile



37

6-amino-4-(2,4-dichlorophenyl)-3-methyl-1,4-dihydropyrano[2,3-c]pyrazole-5-carbonitrile

Fig. 5:. Co_3O_4@SiO_2 –NH_2 Nanocomposites Catalyzed One-Pot Four-Component Synthesis of Pyrano[2,3-C]Pyrazoles.

results urged the authors to pursue the research, in order to establish a deep experimental study.

8. Pyrazole Carboxamides Derivatives

Prabhudeva, *et al*[30] synthesized and developed a new set of pyrazole carboxamides in order to put a new potential agent in place against the bacteria. The antimicrobial activity of the molecules were determined while calculating the minimum inhibitory concentration (MIC) by the method of serial dilution[31] with ciprofloxacine as a positive control, while the antifungal activity has been determined using the nystatine as a positive control. Six pathogenic agents (3 types of bacteria and 3 types of fungi) were the subjects of this study. The obtained results are summarized below in Table 9.

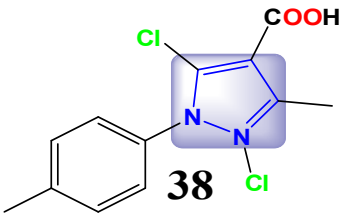
The study showed, at first, that the synthesized compounds 2-pyrazoline carboxamides have an acceptable antimicrobial and antifungal activity with MIC values of 15,0 to 110 gμ/mL (Table 9). Among them, we noted that the compounds 57, 58 and 59 (Figure 9) having the donor substituts and the electron-withdrawing, Chloro, N-dimethyl of the phenyl nucleus. Respectively, this gives, an excellent activity with inhibiting the *S. aureus* germination of the spores (15; 20; 20 μg/ml), *E coli* (25;15; 25 μg/ml), *B. subtilis* (25; 20; 25 μg/ml), *A.niger* (25; 25; 20 μg/ml), *A.flavus* (25; 20; 20 μg/ml), and *C. albicans* (15; 20; 15 μg/ml); they were similar to that indicated by the inhibitory effect of a group of reported compounds.

Then, secondly, the authors deduced that: the compounds 60, 61 and 62 (Figure 9) showed a weaker inhibitory effect between 70–110 μg/ml versus all the tested microorganisms. The weakest inhibitory effect among these compounds may be affected by the presence of fluorine, an electron-withdrawing group such as nitro (–NO2), as well as the larger substitute such as bromine in the phenyl ring, which is in agreement with the data reported previously.[32]

Last but not least, the compounds 63, 64 and 65 (Figure 9) showed a weaker inhibitory effect of *E. coli* (80.0–110.0 μg/ml), *B. subtilis* (85.0–110.0 μg/ml), and *A. flavus* (90.0–110.0 μg/ml). The weaker

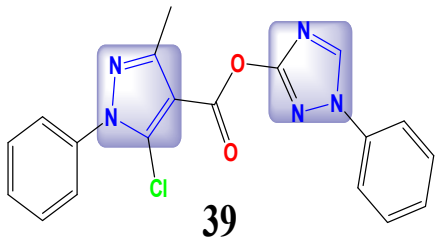
Table 6: Minimum inhibitory Concentration (MIC) of all Compounds (38-45) against Bacteria

Compounds	MIC (µg/mL)					
	R_1	R_2	*S.aureus*	*L.monocytogenes*	*E. coli*	*S.gallinarum*
(38)	CH_3	–	16	32	16	4
(39)	H	H	16	16	8	16
(40)	CH_3	H	4	2	4	0.5
(41)	Cl	F	64	64	64	64
(42)	CH_3	F	8	16	32	32
(43)	H	CH_3	4	8	4	4
(44)	F	CH_3	32	64	32	32
(45)	Cl	CH_3	64	32	64	32
DMSO	Cl	CH_3	>128	>128	>128	>128
CIP			0.125	1	0.5	0.25



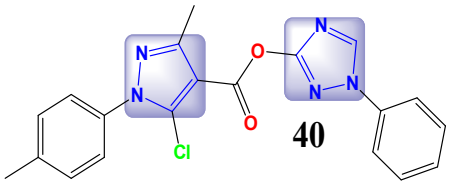
38

2,5-dichloro-3-methyl-1-(*p*-tolyl)-1*H*-2λ^4-pyrazole-4-carboxylic acid



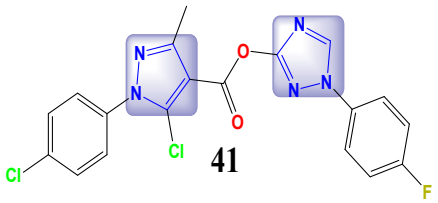
39

1-phenyl-1*H*-1,2,4-triazol-3-yl 5-chloro-3-methyl-1-phenyl-1*H*-pyrazole-4-carboxylate



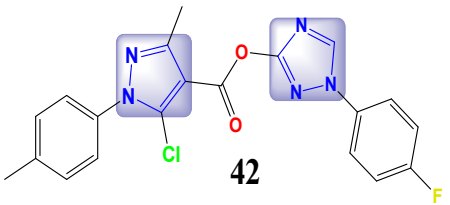
40

1-phenyl-1*H*-1,2,4-triazol-3-yl 5-chloro-3-methyl-1-(*p*-tolyl)-1*H*-pyrazole-4-carboxylate



41

1-(4-fluorophenyl)-1*H*-1,2,4-triazol-3-yl 5-chloro-1-(4-chlorophenyl)-3-methyl-1*H*-pyrazole-4-carboxylate



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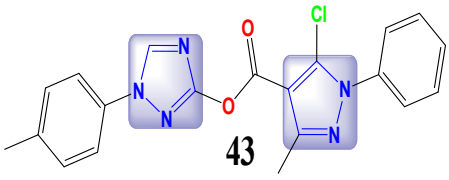
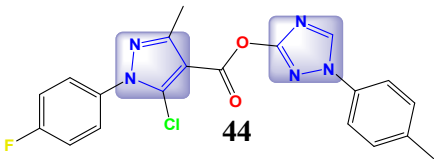


43

1-(*p*-tolyl)-1*H*-1,2,4-triazol-3-yl 5-chloro-3-methyl-1-phenyl-1*H*-pyrazole-4-carboxylate



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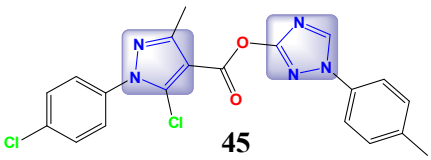


45

1-(*p*-tolyl)-1 *H*-1,2,4-triazol-3-yl 5-chloro-1-(4-chlorophenyl) -3-methyl-1 *H*-pyrazole-4-carboxylate

Fig. 6: Structures of Hydrazone (1-benzylidene-2- (2,5-dimethyl-phenyl) -hydrazine) derivatives versus blue colored bacteria and red colored bacteria

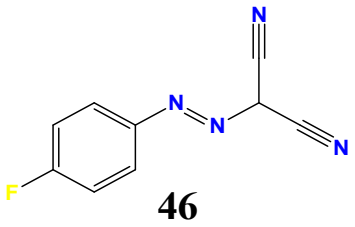
inhibitor effect can be explained by the existence of electron-donor groups, such as: methyl's (–CH3), methoxy (–OCH3), dimethoxy (–O (CH3)2), and chlorine (Cl2) electronegative in aromaticity. This phenomenon is linked to the inhibition of enzymes for these compounds by anchoring studies. However, these compounds showed pleasant activities against S. aureus (30.0 to 40.0 µg/ml), *A.niger* (35.0 to 50.0 µg/ml) and *C. albicans* (35.0 to 45.0 µg/ml).

9 . Pyrazolemethyleneimine, (MPzOAP)

A new tridentate ligand "NNO" based on pyrazole, hydroxyphenylamine methyleneimine (MPzOAP) has been designed and identified through Mandal, *et al.*[33] The complexes multipurpose coordination system was founded through the design of complexes of metal ions Co (III), Ni (II), Cu (II), Zn (II), Cd (II) and Hg (II). The in vitro test is performed to assess the antimicrobial activity of the ligand and metal ion complexes has been reported. The MIC value for the ligand (compound 66) was observed in the range of 50–400g / ml (Table 10).

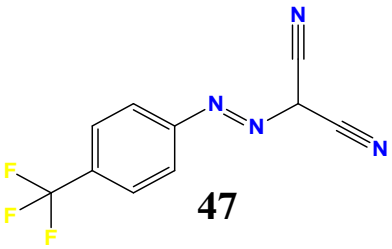
According to a study carried out, the author discovered that the Co (III), Ni (II) and Cu (II) ligands had no remarkable influence on the antibacterial effect. Compound 67 (Figure 10) was apathetic during a concentration of 200 µg/ml, but has antimicrobial capacity compared to several microorganisms, at a MIC value all around 200 and 400 µg / ml and a minimum MIC vis- vis-à-vis Bacillus cereus. 11778. The Cd (II) ligand associated with compound 68 (FIG. 10), the MIC value is very low, around 50 µg / ml for Shigella sonnei NK 4010, *Bacillus cereus* 11778, *Bacillus subtilis* 6633, Micrococcus AGD1, Vibrio cholerae VC20. Then, among the compounds evaluated, compound 69 (FIG. 10) exhibits the best activity with a low MIC value (10 µg/ml) compared with the bacterium *Pseudomonas aeruginosa* 25619, Vibrio cholerae 759, Vibrio cholerae VC20, Micrococcus luteus 10240.

The antibacterial activity of the compounds examined demonstrates that these molecules present a broad spectrum, that is, they are true against both blue- and red-colored organisms, which are more potent compared to enteric organisms.



46

(*E*)-2-((4-fluorophenyl)diazenyl) malononitrile



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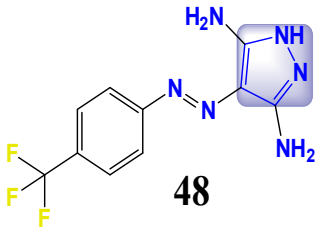
(*E*)-2-((4-(trifluoromethyl)phenyl)diazenyl) malononitrile



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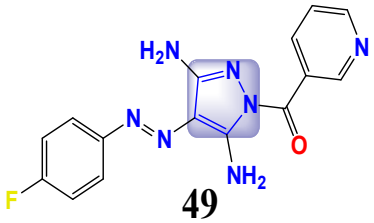
(*E*)-4-((4-(trifluoromethyl)phenyl) diazenyl)-1*H*-pyrazole-3,5-diamine



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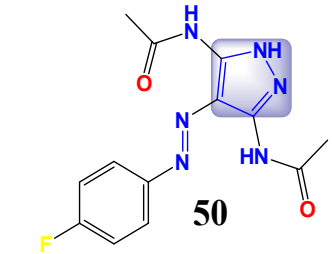
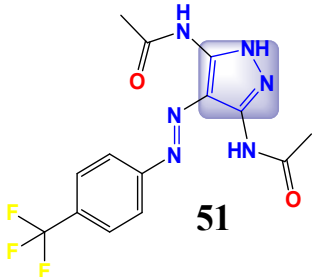
(*E*)-(3,5-diamino-4-((4-fluorophenyl)diazenyl)-1*H*-pyrazol-1-yl)(pyridin-3-yl)methanone



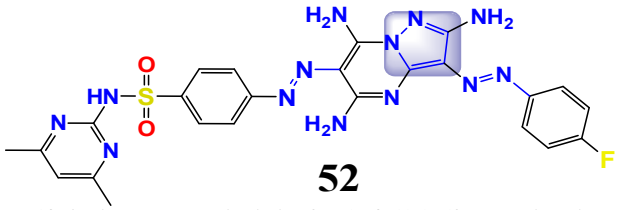
50

(*E*)-*N*,*N*'-(4-((4-fluorophenyl)diazenyl)-1*H*-pyrazole-3,5-diyl)diacetamide



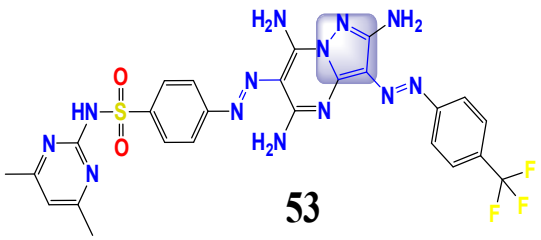
51

(*E*)-*N*,*N*'-(4-((4-(trifluoromethyl)phenyl) diazenyl)-1*H*-pyrazole-3,5-diyl)diacetamide



52

N-(4,6-dimethylpyrimidin-2-yl)-4-((*E*)-(2,5,7-triamino-3-((*E*)-(4-fluorophenyl)diazenyl)pyrazolo[1,5-*a*]pyrimidin-6-yl)diazenyl)benzenesulfonamide



53

N-(4,6-dimethylpyrimidin-2-yl)-4-((*E*)-(2,5,7-triamino-3-((*E*)-(4-(trifluoromethyl)phenyl)diazenyl)pyrazolo[1,5-*a*]pyrimidin-6-yl)diazenyl)benzenesulfonamide

Fig. 7: Pyrazolo [1,5-a] Pyrimidine Derivative Structures versus Blue Colored Bacteria And Red Colored Bacteria.

10. Pyranopyrazoleses

A new set of the innovating therapeutic heterocycle containing the fragments of thiadiazolyl-pyranopyrazole has been synthesized by Reddy, *et al.*[2] All compounds have been tested for their antimicrobial efficiency against four bacteria, and antifungal against two fungi. The minimum inhibitory concentrations (MIC and MBC/MFC) have been measuredand the relation structure-activity (SAR) has also been discussed.

Two bacteria in Gram-positive, such as, *Staphylococcus aureus* ATCC-19433 + *Bacillus subtilis* ATCC-6633, and two bacteria in red color, as *Proteus vulgaris* ATCC-29213 + *Escherichia coli* ATCC-8739, as well as two stumps of *Aspergillus flavus* fungus MTCC-1884+ Aspergillus niger MTCC-1881 have been used for this test. The reported results are in the Table 11 below.

While referring to the Table 11, we note that the compound 71 (Figure 11) provided an exceptional activity against the six pathogenic agents. The possible presence of a substituting nitro on this compound can undoubtedly reinforce the antibacterial activity. Besides, the amalgams 70, 72 and 75 (Figure 11) presented promising antimicrobial results may be explained through the presence of an electron-withdrawing group with the benzene ring, whereas the conjugated 73 and 74 (Figure 11) did not have any effect on all bacterial stumps. The intriguing point that has been observed by the authors is: the active compounds have in common a more important antibacterial efficiency against the bacteria in Gram-negative than the bacteria Gram-positive, and they have a remarkable antifungal activity on A.niger, compared to the other fungus studied.

Thereafter, the authors studied the structrue activity relationship (SAR), in order to know what the influencing groups on the biologic activity are. They distinguished a strong variation of the synthesized compounds activity, even though they have the same nucleuses. The presence of different substituts groups, bounded to fragments, had influence on the biological activity.

According to the authors, the compound 71 showed an exceptional antimicrobial activity, related to the other active compounds, because of the

Table 7: Inhibition Zone in (mm) as a Criterion of Antimicrobial Activity of Some Newly Synthesized Compounds (46–53)

Compounds	Microorganism Inhibition Zone Diameter (mm)								
	Gram positive Bacteria			Gram negative Bacteria			Fungi		
	S. aureus	*B. subtilis*	*S. mutants*	*E. faecalis*	*P. vulgaris*	*E. coli*	*A. fumigates*	*A. flavus*	*C. albicans*
(46)	25	40	22	35	40	28	24	20	21
(47)	22	24	18	25	26	14	NA	NA	NA
(48)	23	23	24	22	23	20	20	13	15
(49)	12	8	NA	11	8	12	NA	NA	NA
(50)	14	16	14	13	20	16	15	9	11
(51)	15	17	19	18	16	13	NA	NA	NA
(52)	18	12	9	13	9	11	NA	NA	NA
(53)	22	23	29	25	26	13	20	17	15

Staphylococcus/ Bacillus/ Strepotococcus/ Enterococcus/ proteus/ Escherichia/ Aspergillus fumigates / Aspergillus ûavus / Candida Albicans.

Table 8: Antibacterial Screening of the Compounds (54–56)

Compounds	Zone of Inhibition (mm)	
	E . coli	*S. aureus*
(54)	19±0.28	17.5±0.58
(55)	9.5±0.68	14.5±0.66
(56)	13.5±0.55	8±0.75
STD for Bac.	Tetracycline (gram +ve)	>19
	Imipenem(gram –ve)	>23

Table 9: Minimum Inhibitory Concentrations (measured in ug/mL) of Thiophene Tethered Pyrazoline Carboxamides against Bacteria and Fungi Species by Serial Dilution Method

Compounds	*S. aureus*	*E. Coli*	*B. subtilis*	*A. niger*	*A. flavus*	*C.albicans*
(57)	15.00±1.0	25.0±0.50	25.0±0.40	25.0±0.60	25.50±0.50	15.0±0.50
(58)	20.0±0.55	15.0±0.40	20.0±0.45	25.0±0.40	20.60±0.60	20.0±0.50
(59)	20.0±0.50	25.0±0.70	25.0±1.00	20.0±0.50	20.0±0.75	15.0±0.50
(60)	70.0±1.50	80.0±1.50	75.0±1.00	75.0±1.25	90.0±1.00	95.0±0.75
(61)	110.0±1.2	105.0±1.0	100.0±1.40	90.0±1.50	80.±1.20	100.0±1.50
(62)	100±1.00	90.0±1.50	80.0±1.00	90.0±1.25	110.0±1.00	110.0±1.50
(63)	40.0±0.50	100.0±1.0	85.0±1.00	40.0±0.55	100.0±0.60	30.0±0.75
(64)	30.0±0.75	90.0±0.70	90.0±1.00	50.0±0.5	90.0±1.40	40.0±1.00
(–65)	40.0±0.50	110.0±1.0	100.0±1.25	35.0±0.60	100.0±1.50	45.0±0.50
CIP	20.0±0.50	20.0±0.75	30.0±1.00	.....	.....	.....
NYS	.....	.....	.....	25.0±0.75	25.0±0.25	20.0±0.50

substitut nitro ($-NO_2$) to the cycle of the benzene's aromaticity that can influence the biologic action. Moreover, they noted that the derivatives 70, 72 and 75 have an excellent antibacterial activity according to the following order 72>70>75 (Figure 12). This is by dint of the attendance of electron-withdrawing groups, such as the fluorine and chlorine atom. The compound 6m revealed a less important anti-microbial activity than the rest. The authors explained this by the substitution to fluorine in Meta position and can act negatively on this activity.

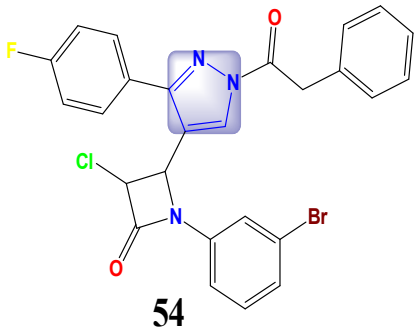
Besides, the compounds attached to the methyl have a slight antifungal action and are inactive when opposed to the bacterial stumps. This means that the methyl group does not have any effect on the anti-bacterial activity.

11. Evaluation of Antimicrobial Activity of Thiazole Heterocycles

A new series of heterocycles based on the thiazole has been synthesized by Abu-Melha, *et al*[34] with the help of cycloaddition reactions 1,3-dipolar, in presence of polyvinylpyridine trans-planted by the chitosan as basic biopolymer catalyst, respecting the environment. The antimicrobial *in vitro* efficiency of the thiazolyl pyrazoles has been studied, while measuring the inhibition zone, and while calculating the minimum inhibitory concentration (MIC).[35]

The antimicrobial activities have been examined versus blue-colored bacteria: Staphylococcus aureus (CMB010010) and Bacillus subtilis (RCMB 010067), and versus red-colored bacteria: Escherichia coli (RCMB 010052), and Proteus vulgaris (RCMB 004 (1) ATCC 13315) with the gentamicin as a control. The antifungal activity has been examined versus Aspergillus fumigatus (RCMB 002008 (4), and Candida albicans (RCMB 05036) with the ketoconazole as a control. The results are presented here in the the following Table 12.

According to Table 12, the authors noted that the synthesized thiazole compounds (Figure 13) presented a good antibacterial effect as opposed to the bacteria Gram-positive *Staphylococcus aureus*, except the compound 79 (Figure 13), and *Bacillus subtilis* except the compound 83. Regarding the red-colored bacteria, all the molecules designed had antimicrobial activity towards *Escherichia coli*. whereas only 76,77 and 83 (Figure 13) were efficient against *Proteus vulgaris*. It is well spread that the thiazole derivative 76 (Figure 13) possessed the most elevated antimicrobial activity, compared to any other examined thiazole towards *Staphylococcus aureus*, *Bacillus subtilis* and *Escherichia coli*. The interesting fact is: the antimicrobial activity of this family comes closer to the gentamicin power against the examined red-colored bacteria. Besides, the derivative 77 (Figure 13) exercised the most important antimicrobial activity versus *Proteus vulgaris*, while all synthesized compounds had no antifungal activity against *Aspergillus fumigatus* or



54

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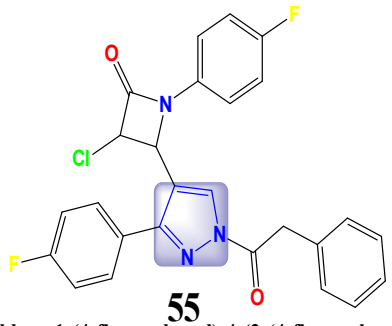

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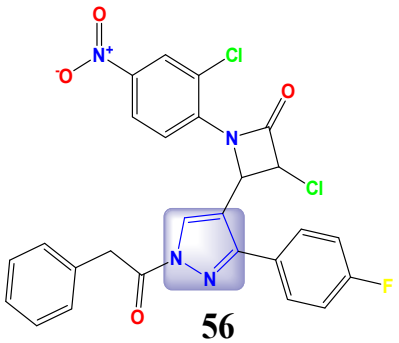
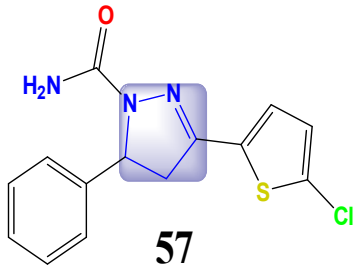
3-chloro-1-(4-fluorophenyl)-4-(3-(4-fluorophenyl)-1-(2-phenylacetyl)-1*H*-pyrazol-4-yl)azetidin-2-one



56

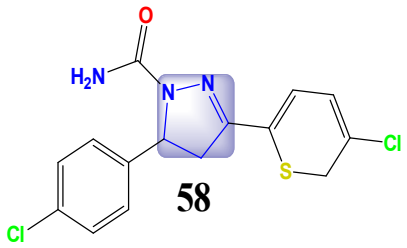
3-chloro-1-(2-chloro-4-nitrophenyl)-4-(3-(4-fluorophenyl)-1-(2-phenylacetyl)-1*H*-pyrazol-4-yl)azetidin-2-one

Fig. 8: 2-Azetidinone Capped Pyrazole Derivative Structures versus Blue Colored Bacteria and Red Colored Bacteria



57

3-(5-chlorothiophen-2-yl)-5-phenyl-4,5-dihydro-1*H*-pyrazole-1-carboxamide



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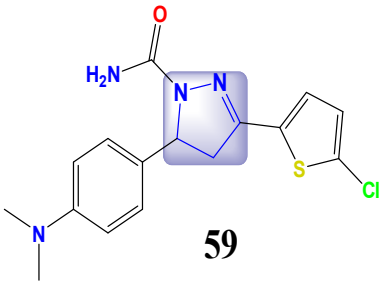
3-(3-chloro-2*H*-thiopyran-6-yl)-5-(4-chlorophenyl)-4,5-dihydro-1*H*-pyrazole-1-carboxamide



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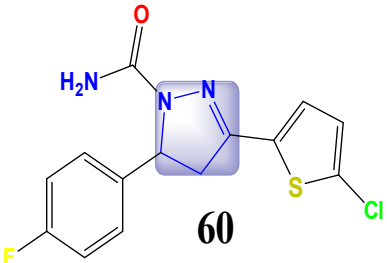


60

3-(5-chlorothiophen-2-yl)-5-(4-fluorophenyl) -4,5-dihydro-1*H*-pyrazole-1-carboxamide

Candida albicans. Judging by these data, we have to say that the attendance of ethoxycarbonyl groups and the p-tolyl as substitut on the pyrazole nucleus enhance the antimicrobial activity of the molecule 76 (Figure 13).

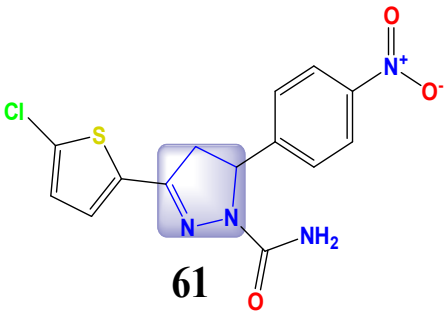
12. Pyrazoles, pyrazolone and Enaminonitrile Pyrazole Derivatives

Sayed, *et al*[36] developed a novel set of pyrazolone and enaminonitriles pyrazole. The prepared compounds have been tested, as antibacterial agents, versus various bacterial stumps blue-and red-colored, while calculating the minimum inhibitory concentration (MIC), as well as the inhibition zone.[37] The results shown the Table 13.

According to Table 13, the authors prove that the anti-microbial activity of designed compounds versus red-colored bacteria was weaker compared to their potential, blue-colored bacteria. This is explained by the chemical nature of the external cellular membranes for the two kinds of bacteria: red-colored bacteria described by a solid and reticulate cellular wall that resists the permeation of the various biocides in the cellular nucleus, while the Gram positive bacteria has a thin cellular membrane that permits the easy penetration of the biocides in the cellular nucleus.[38]

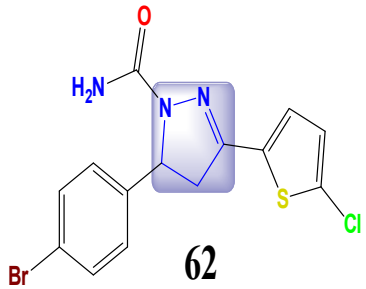
Authors reported that the action of the synthesized hetercyclic molecules have been suggested as a way of adsorption. The different molecules have the heteroatomes that contain doublets of electrons as well as nitrogen or oxygen atom. Then, the centers are rich with electrons containing double bonds (Figure 15), phenyl nucleuses, and triple links of the cyano (CN).[39]

The penetrated molecules 84-89 (Figure 14) in the nucleus initiated various interactions inside the cell, especially the denaturation of the proteins and the coordination complexes by the DNA within the nucleus. These interactions disrupt the biologic activity of the microorganisms and result in the death of the bacterial cells. The following order: 88>86>87>89>85>84 (Figure 14) classifies the antimicrobial potential to the designed compounds from the more to the less powerful.



61

3-(5-chlorothiophen-2-yl)-5-(4-nitrophenyl) -4,5-dihydro-1*H*-pyrazole-1-carboxamide



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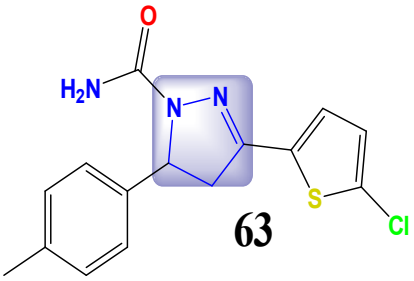
5-(4-bromophenyl)-3-(5-chlorothiophen-2-yl)-4,5-dihydro-1*H*-pyrazole-1-carboxamide



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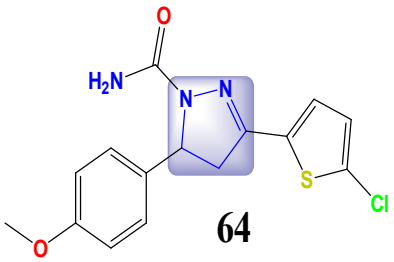
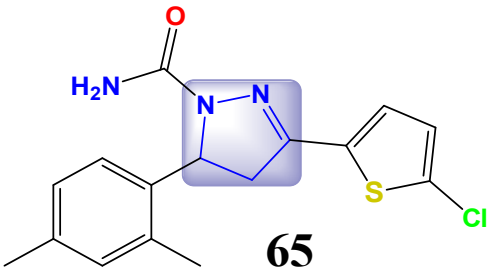


64

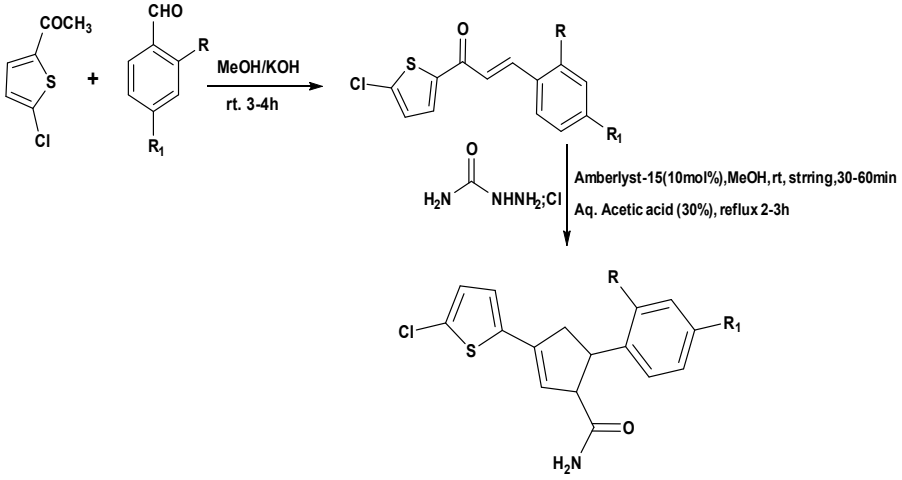
3-(5-chlorothiophen-2-yl)-5-(4-methoxyphenyl) -4,5-dihydro-1*H*-pyrazole-1-carboxamide



65

3-(5-chlorothiophen-2-yl)-5-(2,4-dimethylphenyl)-4,5-dihydro-1*H*-pyrazole-1-carboxamide

Fig. 9: Structures of Pyrazole Carboxamides Derivatives showed best Antibacterial Activity

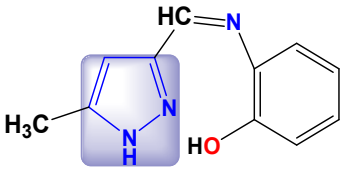


13. Alkylaminopyrazoles derivatives

A new series based on Mannich substituted aminohexadecan has been designed according to Zalaru, *et al.*[40] The antibacterial activity of the designed molecules has been examined versus blue-colored strains (*Bacillus subtilis* ATCC 6633, *Staphylococcus aureus* ATCC 25923), and red-colored strains (*Klebsiella* pneumoniae ATCC13420, *Pseudomonas aeruginosa* ATCC 27853, *Escherichiacoli*ATCC 25922), while comparing their inhibitory concentration values (MIC) to a classic medicine as: the erythromycin; the anti-fungal activity has been tested against *Candida albicans* with clotrimazole as a reference. The obtained results are shown in Table 14. It has been observed that the DMSO solvent does not impact the antibacterial activity of the examined compounds.

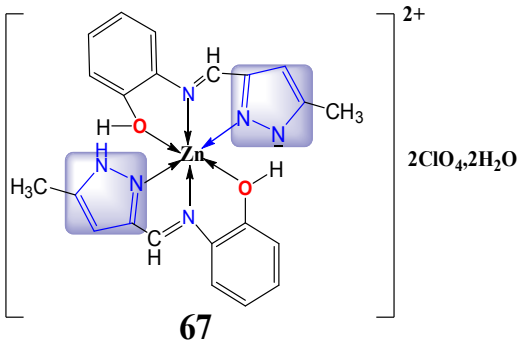
The compound 91 (Figure 18) presented the best important activity versus *Bacillus subtilis* (MIC=0.007 μgml^{-1}), and it has been noted that compounds 90 and 94 (Figure 18) were twice more active than the standard (MI=0,031 μgml^{-1}). The compounds 90, 94 and 95 (Figure 18) were also twice more active than the classic(MIC=0,031 μgml^{-1}) versus *Staphylococcus aureus*. All the compounds had an important activity versus *Klebsiella pneumoniae*, and *Pseudomonas aeruginosa*. The compound 94 revealed to be twice more active than the stallion (MIC=0,031 μgmL^{-1}) against *Escherichia coli*. The least activity has been observed on the compound 92 versus *Staphylococcus aureus*, *Klebsiella pneumoniae*, *Pseudomonas aeruginosa*, and *Candida albicans*. The compound 94 was less active, particularly on the *Bacillus subtilis*, *Staphylococcus aureus*, and *Escherichia coli* stains.

Structrurally, the molecule 91 presented most elevated activity versus *Bacillus subtilis*, possess an atom of iodine (I) in position 4 of the pyrazole cycle. The molecule 92, minimum apathy, possess a nitro group (-NO) in position 4 of the pyrazole nucleus. The molecule 93 is active as the stallion versus the bacterial microorganisms blue- and red-colored. It contains hydrogen in position 4 of the nucleus 3,5 dimethylpyrazole.



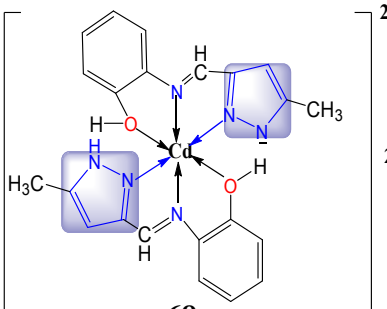
66

(*Z*)-2-(((5-methyl-1*H*-pyrazol-3-yl)methylene)amino)phenol



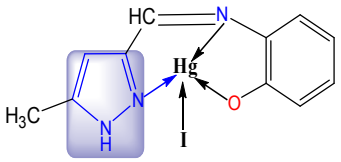
67

Perchlorate-bis-(5-methylpyrazole-3yl-N-(2'-hydroxyphenylamine) methyleneimine aquo zinc (III) dihydraté



68

Perchlorate-bis-(5-methylpyrazole-3yl-N-(2'-hydroxyphenylamine) methyleneimine aquo cadmium (II) trihydraté



69

(5-methylpyrazole-3yl-N-(2'-hydroxyphenylamine) methyleneimine aquo mercure dihydraté

Fig. 10: Structures of Pyrazolemethyleneimine Derivatives, (MPzOAP) versus Blue Colored Bacteria and Red Colored Bacteria.

Table 10: Minimum Inhibitory Concentration (MIC) of MPz OAP (66); [Zn(MPz OAP)$_2$](ClO$_4$)$_2$,2H$_2$O (67); [Cd(MPz OAP)$_2$](ClO$_4$)$_2$.3H$_2$O (68) and [Hg(MPzOAP)I].2H$_2$O (69)

Organism	(66)	(67)	(68)	(69)
S. sonnei NK 4010	100	400	50	25
B. cereus 11778	100	50	25	
B. subtilis 6633	50	–	50	50
Micrococcus AGDI	50	400	50	25
B. pumilus 14884	50	–	100	50
V. cholerae 759	50	–	–	10
V. cholerae VC20	50	–	50	10
B. polymyxa 4747	100	–	100	50
S. choleraesuis	400	400	200	25
Providencia	–	400	400	50
B. bronchiseptica 4617	–	400	200	25
Salmonella 14669	–	400	400	50
E. coli K88	–	–	–	50
S. typhimurium NCTC 74	–	–	–	50
P. aeruginosa 25619	–	–	–	10
K. pneumoniae 10031	–	–	–	50
S. aureus 10031	–	–	–	25
M. luteus 10240	–	–	–	10

"–" shows no measurable zone of inhibition.

With reference to Table 14, we noticed that the compounds 90 to 95 presented an antifungal activity twice weaker than the clotrimazole against Candida albicans, whereas the rest were less vigorous.

14. Pyrazole-1-carbothioamide

The pyrazoline presents various biological activities, such as anti-microbial,[41,42] antifungal,[43] etc. Abdelhamid, *et al*[44] proceeded to the novel thiazoles, thiadiazoles, and pyranothiazole carbothioamide synthesis. They have been tested to assess antibacterial activity versus *Streptococcus pneumoniae, Bacillus subtilis, Pseudomonas aeruginosa,* and *Escherichia coli* and anti-fungal against *A. fumigatus* and *C.albicans*. The obtained results are summarizes in Table 15.

14.1. Inside the Thiazolylpyrazoles

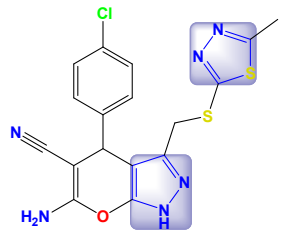
The methyl (–CH$_3$), and phenylimine (–N=NPh) groups substitution in the compound 96 and the the OH, and phenyl imine (–N=NPh) groups substitution in the compound 97 (Figure 19) in the positions 3 and 4 repectively in the pyrazole nucleus did not have any activity versus any examined blue-colored bacteria and red-colored bacteria. However, they had an activity curbed versus the tested fungus.

The substitution of the groups OH and -N=NPh in the compound 98 (Figure 19) in positions 3 and 4 in the pyrazole nucleus showed a powerful effect against all types of tested bacteria and fungus.

The introduction of the groups CH$_3$, and 4-CH$_3$C$_6$H$_4$N=N in the compound 97 (Figure 19) in position 3 and 4 in the pyrazole nucleus indicate an important impact versus the red-colored, blue-colored bacteria, and the fungus.

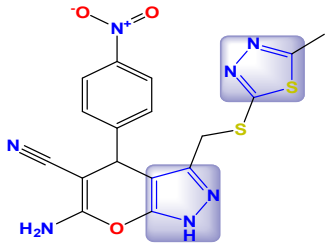
14.2. Inside the Thiazolylthiadiazole Carbohydrazide (99–101)

The introduction of the C$_2$H$_5$CO$_2$ group in the derivative 99 (Figure 19) in position 2 in the 1,3,4-thiadiazole nucleus showed a significant effect against the Af fungus, as well as a curbed activity versus the blue-colored bacteria, red-colored bacteria and the CA fungus.



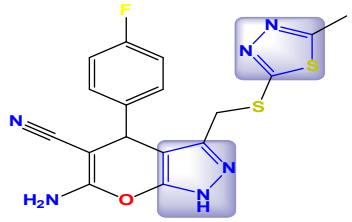
70

6-amino-4-(4-chlorophenyl)-3-(((5-methyl-1,3,4-thiadiazol-2-yl)thio)methyl)-1,4-dihydropyrano[2,3-*c*]pyrazole-5-carbonitrile



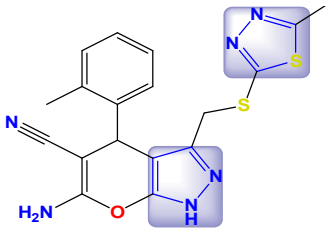
71

6-amino-3-(((5-methyl-1,3,4-thiadiazol-2-yl) thio)methyl)-4-(4-nitrophenyl)-1,4-dihydropyrano[2,3-*c*]pyrazole-5-carbonitrile



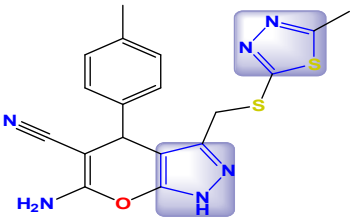
72

6-amino-4-(4-fluorophenyl)-3-(((5-methyl -1,3,4-thiadiazol-2-yl)thio)methyl)-1,4-dihydropyrano[2,3-*c*]pyrazole-5-carbonitrile



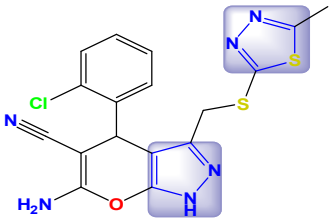
73

6-amino-3-(((5-methyl-1,3,4-thiadiazol-2-yl) thio)methyl)-4-(*o*-tolyl)-1,4-dihydropyrano [2,3-*c*]pyrazole-5-carbonitrile



74

6-amino-3-(((5-methyl-1,3,4-thiadiazol-2-yl) thio)methyl)-4-(*p*-tolyl)-1,4-dihydropyrano [2,3-*c*]pyrazole-5-carbonitrile



75

6-amino-4-(2-chlorophenyl)-3-(((5-methyl-1,3,4-thiadiazol-2-yl)thio)methyl)-1,4-dihydropyrano[2,3-*c*]pyrazole-5-carbonitrile

Fig.. 11. Pyranopyrazole Derivative Structures versus Blue Colored and Red Colored Bacteria.

Table 11: The MIC(MBC/MFC) of Compounds (70–75)

Compounds	MIC(MBC/MFC)					
	S. aureus	*B. subtilis*	*P. vulgaris*	*E. coli*	*A. flavus*	*A. niger*
(70)	25 (200)	50 (>200)	25 (100)	50 (>200)	100 (>200)	50 (>200)
(71)	25 (100)	12.5 (100)	50 (100)	12.5(25)	50 (200)	12.5 (25)
(72)	50 (200)	25 (200)	100 (>200)	100 (200)	25 (100)	25 (50)
Ciprofloxacin	12.5	12.5	12.5	6.25	–	–
Ketoconazole	–	–	–	–	12.5	6.25

The grouped fixation CH_3CO in the derivative 100 (Figure 19) in position 5 in the 1,3,4-thiadiazole nucleus part presented a strong impact versus the A. fungus, a curbed activity versus the blue-colored, red-colored bacteria, and the CA fungus.

The substitution of the C_6H_5CONH group 101 (Figure 19) in position 2 of the 1,3,4-thiadiazole fragment contributed with a strong impact versus fungi, a curbed activity versus blue-colored bacteria, red-coloured bacteria and the CA.

14.3. Inside the thiazolylpyridazine-3,6-dione (22)

The introduction of the group carbonyl-1,2-dihydropyridazine-3,6-dione in location 5 to the thiazole cycle had a powerful impact against the Af fungus and a curbed activity against the bacteria.

15. Quinolines Derivatives Bearing Pyrazole Moiety

An exploration study has been done by El Shehry, *et al*[45] in order to develop some new antimicrobial agents. Three sets of quinoline derivatives with a paryzole fraction has been synthesized. The synthesized compounds were examined and tested for their antibacterial and antifungal activities.

In order to test the antibacterial activity, the researchers have chosen the use of the following stains: three blue-colored bacteria, Staphylococcus aureus (RCMB 010027), *Staphylococcus epidermidis* (RCMB 010024), and *Bacillis subtilis* RCMB 010063; three red-colored bacteria, *Proteous vulgaris* (RCMB 010085), a *Klebsiella pneumonia* (RCMB 010093), and *Shigella flexneri* (RCMB 0100542) as a referential medicine: Ampicillin, and Gentamycin. The antifungal activity has been evaluated, using three fungus strains that are: *Aspergillus fumigatus* (RCMB 02564), *Aspergillus clavatus* (RCMB 02593), 05035) with *Amphotericin* as a referential medicine.

The tests have been made while the serial double dilution.[46] The results are reported in Table 16.

The results explain that the most of the designed molecules presented various classes of inhibition, versus the panel essay of species. The pyrazole derivative 111 (Figure 20) exposed best results compared to the referential medicines as its MIC values revealed (0,12-0,98 µg/mL). It is about a quadriple power versus *B. subtilis*, *P. vulgaris*, *S. flexneri*, and *C. albicans*, if we compare it to the referential medicine.

Besides, the derivative 104 (Figure 20) showed a more powerful MIC in comparison to the standard, versus *S. epidermidis*, and similar to the standard against *S. flexneri*, and *C. albicans*.

The pyrazole derivative 107 (Figure 20) is equal to the amphotericin, versus the development of A. fumigatus, and of *C. albicans* respectively, with a MIC value of 0,98 and 0,49 µg/ml. However, it presented an activity reduced to 50%

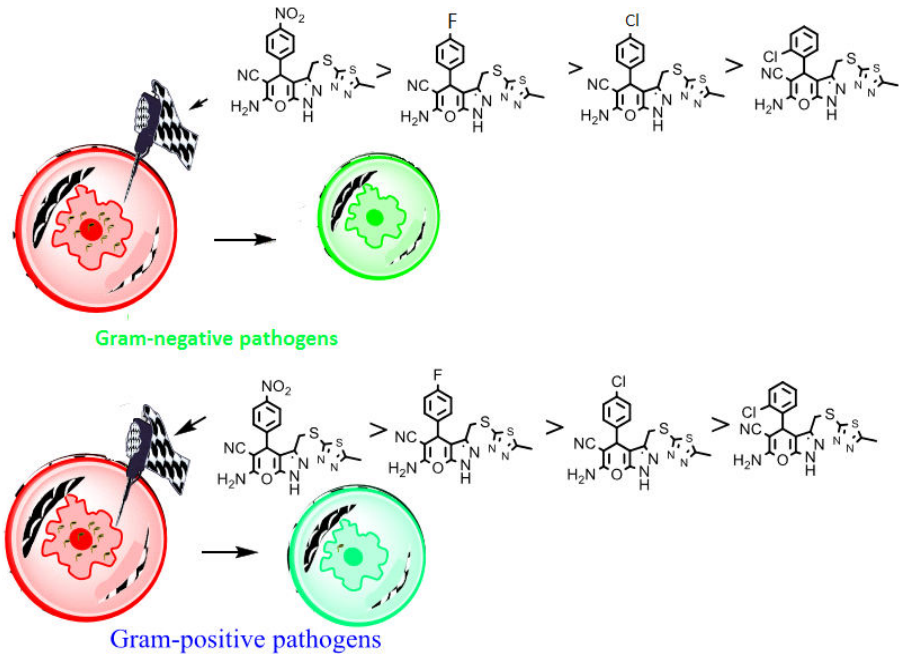


Fig. 12: Compounds Activity versus Blue and Red Colored Bacteria.

Table 12: Antimicrobial Activities of the newly Synthesized Thiazoles was shown as Minimum Inhibitory Concentration (MIC) in µg/mL of the Tested Microorganisms

Compounds	Fungi		Gram-positive Bacteria		Gram-negative Bacteria	
	A. fumigatus	*C. albicans*	*S. aureus*	*B. subtilis*	*E. coli*	*P. vulgaris*
(76)	NA	NA	78.13	396	156.25	315
(77)	NA	NA	1250	5000	156.25	312.5
(78)	NA	NA	5000	2500	2500	5000
(79)	NA	NA	NA	1250	10,000	5000
(80)	NA	NA	312.5	1250	625	1250
(81)	NA	NA	625	1250	1250	312.5
(82)	NA	NA	625	2500	2500	5000
(83)	NA	NA	10,000	NA	5000	NA

NA: No activity. Experiment was done using the diffusion agar method.

compared to the ampicillin versus *S. epidermidis* (MIC: 0,98 µg/ml). Last but not least, the derivative 103 (Figure 20) showed a double power compared to the gentamicin against the *P.vulgaris* growth (MIC 0.97 µg/ml).

16. Pyrazole and Pyrimidine Derivatives

Farag and Fahim[47] synthesized a new set of pyrazole and pyrimidine and examined for their antibacterial, and antifungal activity, mininum inhibitory concentration (MIC), using four fungus: A. fumigates (RCMB 02568), *Candida albicans* (RCMB 05036), *Syncephala strumracemosum* (RCMB 05922), and *Geotricum candidum* (RCMB 05097), two blue-colored bacteria: *S. pneumonia* (RCMB 010010), and *B. subtilis* (RCMB 010069), two red-colored bacteria: *P. aeruginosa* (RCMB 010043), and E. coli (RCMB 010052). The results have been summarized in Table 17.

The compound 112 (Figure 21) and 113 have, nearly, the same biologic activity. We have noticed that the carboxyl group incorporation in the following compounds 117, 112, 113, and 116 (Figure 21) exposed a higher antimicrobial than other derivatives. The compounds 115, 114 (Figure 21) present curbed activities versus any stains. These results show that the other more voluminous substituents reduce the antibacterial activity. Geotricum candidum is mainly accountable for the increase in the pervasive aspergillosis (IA) incidence on the immunodeficiency patient.[48] Besides, the death rate due to the pervasive fungal infections is not allowed due to number of antifungal medication.[49]

17. Pyrazole-4-carboxaldehydes Derivative

According to the research,[50] and to the purpose of new powerful anti-microbial agents conception, Puthran, *et al*[51] described the Schiff base synthesis containing the substituted hybridized thiophene with pyrazole-4-carbaldehydes derivatives in 1,3. The synthesized products, as such, have been tested for anti-bacterial and anti-fungal activity.

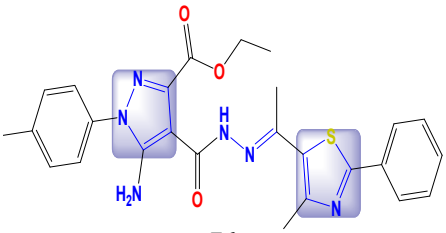
The antimicrobial activity has been tested versus two blue-colored bacteria (*B. subtilis*) and red-colored bacteria (*E. coli*) stains (*S. aureus*). However, the anti-fungal activity has been tested versus only one fungal stain (*C. albicans*), while calculating the MIC. The Table 18 represents the obainted results.

While analyzing Table 18, researchers deduced that the compounds 118, 120, and 121 (Figure 22) showed respectively MIC values of 31,25, 31,25> 125 µg/ml versus B. subtilis. The other compounds 119 and 122 (Figure 22) showed an activity inhibition of C. albicans with MIC values included between 62,5>125 µg/ml).

It has been reported that the pyrazoles containing the substituted thiophene of the Schiff base derivatives by electron-withdrawing groups showed a good activity against the bacterial, and antifungal stains.

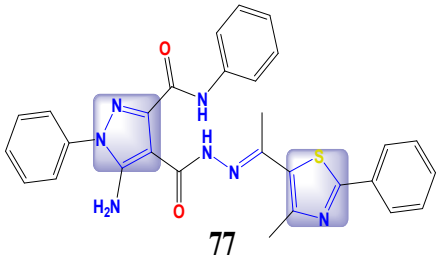
18. Pyrazole-benzofurans Hybrids

Sanad, *et al*[52] synthesized a set basis on hybrid pyrazole-benzofuran in order to make new potential antimicrobial and antifonfungal. The biologic activity has been determined by the diffusion method on agar's well [53]. The bacteria chosen by this team to test are: *Staphylococcus aureus* (ATCC: 6538), *Streptococcus mutans* (ATCC: 25175) as blue-colored



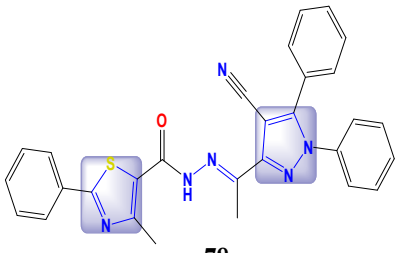
76

ethyl (*E*)-5-amino-4-(2-(1-(4-methyl-2-phenylthiazol-5-yl)ethylidene)hydrazine-1-carbonyl)-1-(*p*-tolyl)-1*H*-pyrazole-3-carboxylate



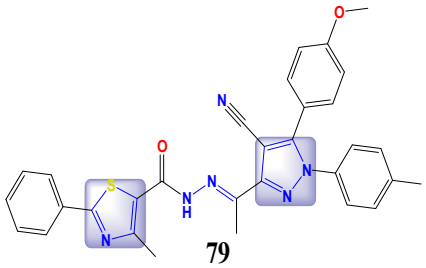
77

(*E*)-5-amino-4-(2-(1-(4-methyl-2-phenylthiazol-5-yl) ethylidene)hydrazine-1-carbonyl)-*N*,1-diphenyl-1*H*-pyrazole-3-carboxamide



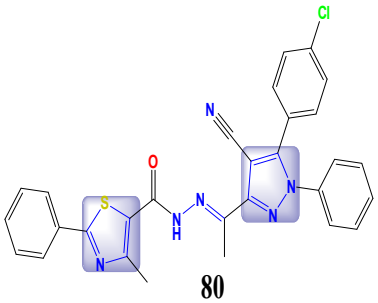
78

(*E*)-*N*'-(1-(4-cyano-1,5-diphenyl-1*H*-pyrazol-3-yl)ethylidene)-4-methyl-2-phenylthiazole-5-carbohydrazide



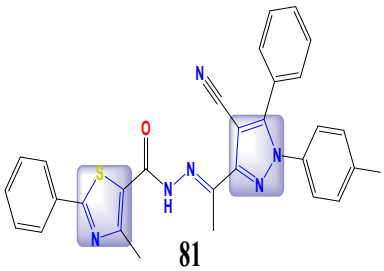
79

(*E*)-*N*'-(1-(4-cyano-5-(4-methoxyphenyl)-1-(*p*-tolyl)-1*H*-pyrazol-3-yl)ethylidene)-4-methyl-2-phenylthiazole-5-carbohydrazide



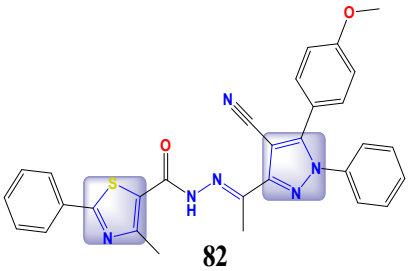
80

(*E*)-*N*'-(1-(5-(4-chlorophenyl)-4-cyano-1-phenyl-1*H*-pyrazol-3-yl)ethylidene)-4-methyl-2-phenylthiazole-5-carbohydrazide



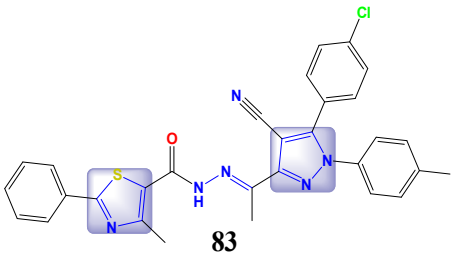
81

(*E*)-*N*'-(1-(4-cyano-5-phenyl-1-(*p*-tolyl)-1*H*-pyrazol-3-yl)ethylidene)-4-methyl-2-phenylthiazole-5-carbohydrazide



82

(*E*)-*N*'-(1-(4-cyano-5-(4-methoxyphenyl)-1-phenyl-1*H*-pyrazol-3-yl)ethylidene)-4-methyl-2-phenylthiazole-5-carbohydrazide



83

(*E*)-*N*'-(1-(5-(4-chlorophenyl)-4-cyano-1-(*p*-tolyl)-1*H*-pyrazol-3-yl)ethylidene)-4-methyl-2-phenylthiazole-5-carbohydrazide

Table 13: Antimicrobial Activities of the Synthesized Compounds (84–89)

Compounds	Gram positive Bacteria		Gram negative Bacteria		Fungi
	B. subtilis	*S. aureus*	*P. aeruginosa*	*E. coli*	*A. niger*
(84)	NA	NA	NA	NA	NA
(85)	18.1	16.4	17.4	15.3	15.2
(86)	23.5	21.4	19.1	22.4	21.3
(87)	23.5	20.3	17.9	22.1	20.6
(88)	25.3	23.2	19.3	23.1	25.5
(89)	21.3	19.3	17.6	20.6	19.3
Standard	18	18	18	17	12

bacteria and *Escherichia coli* (ATCC: 9637), *Klebsiella pneumonia* (ATCC: 10031) as red-colored bacteria.

The MIC values has been achieved for the examined compounds presenting inhibition zones >10mm. The MIC values have been determined by a serial method of dilution twice.[54] The obtained results are summarized in Table 19.

While analyzing these results (Table 19), the author noted that the MIC values of the compound 124 (Figure 23) were respectively 7.8; 15.6 µg/ml versus *S. aureus* and *S. mutans,* and therefore, more important than the standard ampicillin that is 62,5 µg/mL. This same compound presented MIC values of 3.9; 15.6 µg/ml versus *K. pneumoniae,* and *E. coli,* which is much more important than the standard gentamicine (62.5; 31.25 µg/ml). This makes the compound as the most efficient candidate among the tested panel.

Then, the compounds 123, 125 and 127 (Figure 23) showed a curbed activity versus Streptococcus mutans in comparison to the standard medicine ampicillin. The rest of the compounds showed an average antibacterial activity.

Structure-activity Relationship (SAR)

The structure-activity relationship (SAR) study has been realized to establish how the substituent on the phenyl nucleus and the pyrazol compounds affect the antimicrobial activities. The results prove the different activities between the derivatives carrying different substituent and the pyrazole derivatives of the phenyl nucleus external position indicating the substituent effect on the resulted activity.

The activity of such derivatives could be affected by the presence of methyl ($-CH_3$) or methoxy ($-OCH_3$) groups as electron-donating groups in phenyl nucleus external position. The compound 124 is substituted by a methyl group ($-CH_3$) electron donor bound to phenyl group of the pyrazol cycle, which showed topmost antibacterial activities. These activities can be assigned to the electronic density of this compound.

19. Coumarin-pyrazole Carboxamide

The coumarin is an aromatic substance forming a large class of

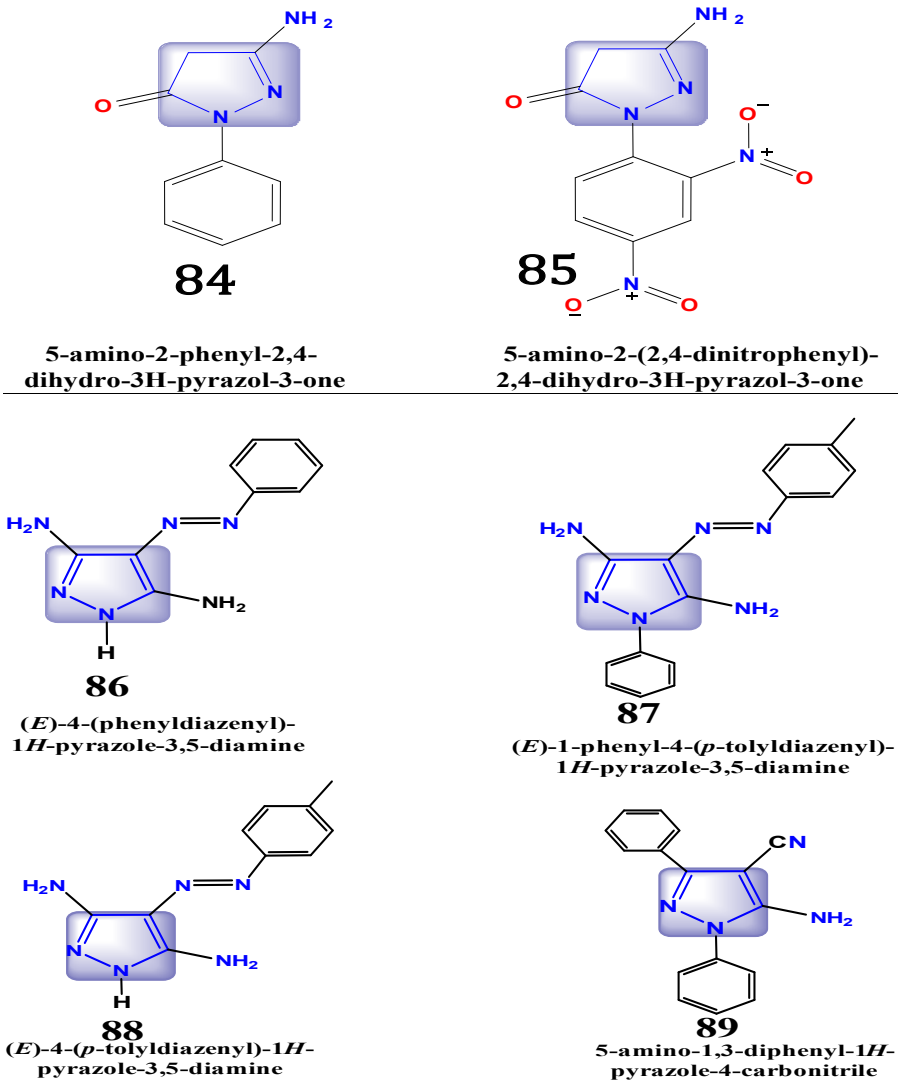


Fig.14: Pyrazole Derivative Structures, Pyrazolone and Enaminonitrilepyrazole Derivatives versus Blue Colored and Red Colored Bacteria.

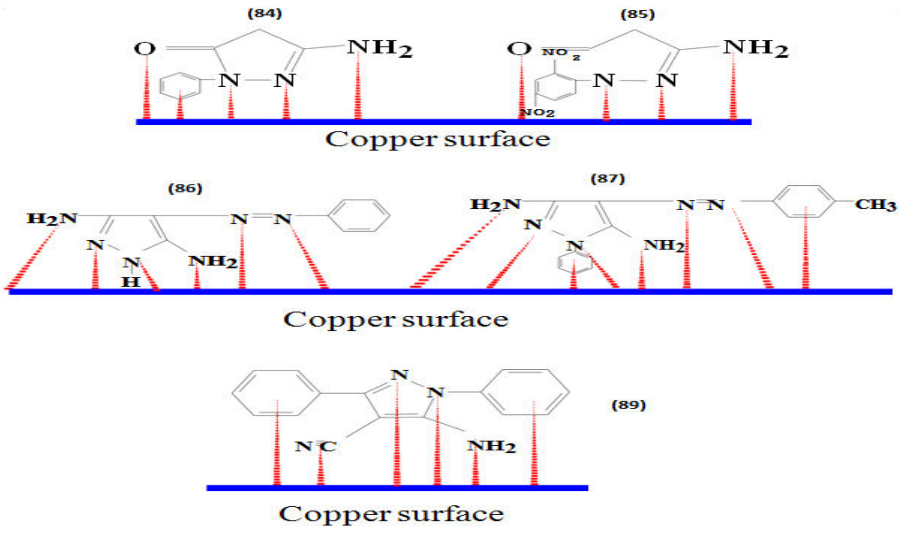


Fig. 15: Mechanism of Action of the Proposed Adsorption of various Heterocyclic Molecules on the Surface of Copper.

extensively present natural products as secondary metabolism of plants. Right now, there are[55,56] more than 1800 natural, different, discovered, and described coumarins. A lot of them present an important biologic activity as anti-fungal,[57] antibacterial,[58] antimicrobial,[59] and many others. Because of its high natural bioactivité, Liu, *et al*[60] synthesized and developed new therapeutic agents based on coumarin-pyrazole carboxamide.

The synthesized compounds have been tested for their antibacterial activity versus two blue-colored bacteria as: *Staphylococcus aureus*, and *Listeria monocytogenes*, as well as two red-colored bacteria: *Escherichia coli*, and *Salmonella*. The novobiocin, ciprofloxacin have been used as a reference. The results obtained are summarized in Table 20.

According to the results contained in Table 20, the authors deduced that the R_3 group, substituted by chlorine on the benzene nucleus improves the antibacterial activity of the designed compounds. Besides, the introduction of diethylamino set 133–134 (Figure 24) on the R_2 group showed considerable improved effects compared to other series.

For Listeria monocytogenes, when the R_4 position was substituted through an ester group or a carboxyl, the biologic activities of the compounds 129 and 131 (Figure 24) presented an improved antibacterial activity compared to other compounds.

Towards *Escherichia coli*, when the R_1 position was replaced by other entities, the antibacterial activity was more important; and when R_1 represents chlorine (Cl), 131 (Figure 24), it generates an excellent value of MIC.

For *Salmonella*, the R_4 group is substituted by the carboxyl or ester. Their antibacterial activities are curbed. Then, when the R_1 group represents the bromine (Br) and the group R_4 cyano (CN), 130 (Figure 24), it shows an excellent antibacterial effect.

Futhermore, the authors have concluded that after the structure-activity relationship (SAR) study between the sets, antibacterial activity is reduced when they introduced electron-

Table 14: Antibacterial and Antifungal Activities of Compounds (90-95) against Bacterial and Fungal Strains in MIC (µgmL^{-1})

Compounds	*B.subtilis*	*S. aureus*	*K. pneumoniae*	*P. aeruginosa*	*E. coli*	*C. albicans*
(90)	0.031	0.031	0.125	1	0.062	1
(91)	0.007	0.125	0.062	1	0.125	0.25
(92)	0.062	0.5	1	1	0.062	0.125
(93)	0.062	0.062	0.062	0.062	0.062	0.062
(94)	0.031	0.031	0.062	0.062	0.031	0.062
(95)	0.062	0.031	0.062	0.062	0.062	0.062
ERY	0.062	0.062	0.062	0.062	0.062	n/a
CLO	n/a	n/a	n/a	n/a	n/a	0.031

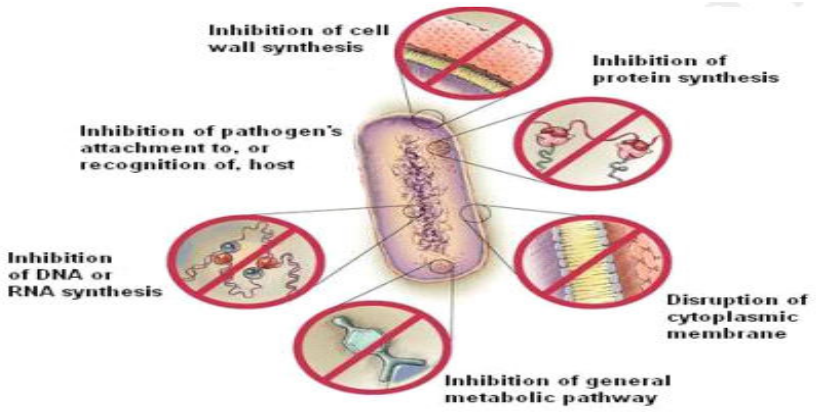


Fig. 17: Different Mechanisms of action of Antimicrobial Agents

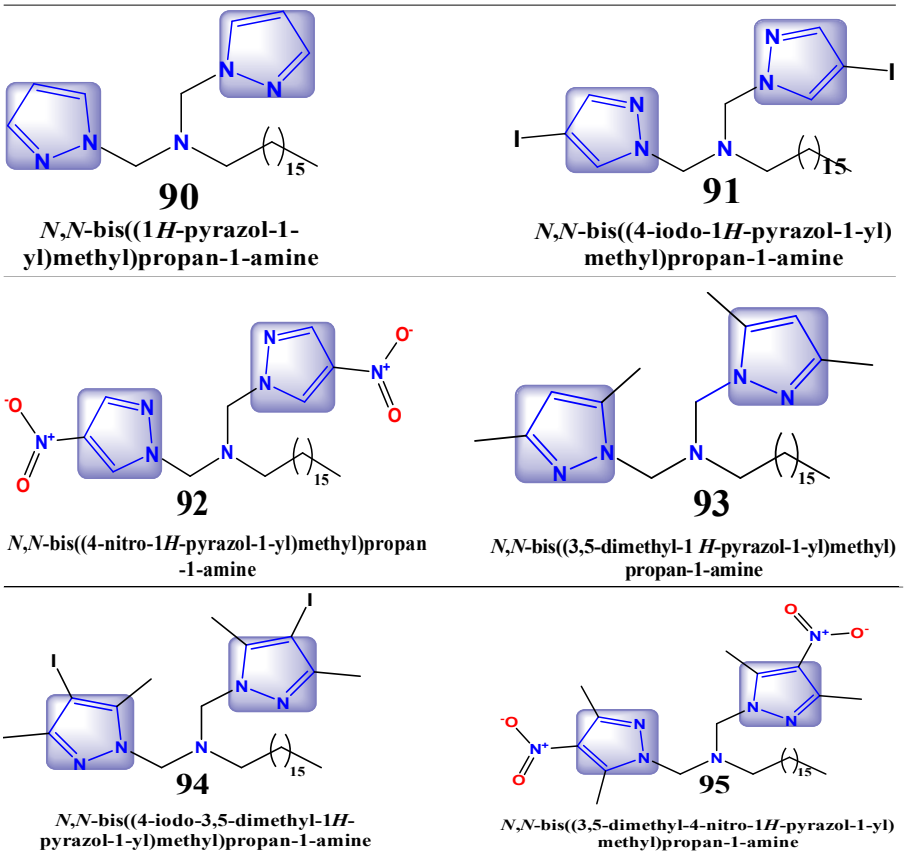


Fig. 18: Structures of Alkylaminopyrazole Derivatives versus Blue Colored and Red Colored Bacteria

withdrawing groups nitro (CN). Besides, the compounds 133 and 134 (Figure 24) showed signficantly improved effects against Salmonella in comparison to the other sets. Their difference resides in the introduction of the diethylamino, in a way that they believe that the diethylamino can act as special pharmacophore for the inhibition of Salmonella.

DISCUSSION

Based on the results obtained from various pyrazole and its derivative, as an antibacterial and antifungal agent, we can affirm that the development of bioactive molecules from pyrazole became essential. Indeed, the synthesis of chitosan extracted from the natural resource showed a promising anti-microbial and antifungal effect against bacteria and fungi. Compound 2 (Figure 2) presented a high inhibitory efficiency (6.25 µg/ml) due to the fact that the pyrazole ring substituted in position 5 by the electron-withdrawing –Cl group. Then, the development of an organo-metallic complex based on ferrocene showed a medium efficiency. Compound 9 (Figure 3) showed a moderate efficiency in spite of the substitution of pyrazole ring by the electron-donor group as methoxy (the electron-withdrawing group NO2 decreases the biological activity compared to the reference. See Table 2 page 9). Furthermore, compounds 29 and 30 (Figure 4) (MIC=25 µg/ml) are based on pyrazolo pyridazin which showed a better inhibitory efficiency against Gram-Positive bacteria B. subtilis and *S. aureus*. These conjugates presented electro-actractive substituents like -Cl and -F can increase the inhibitory activity as well as the 2,5 dimethylphenyl substituted pyrazole ring. However, these compounds showed moderate activity against Gram-Negative bacteria.

On the other hand, the pyrazole ester derivatives 40 and 43 (Figure 6) showed a better biological activity (MIC=4µg/ml) compared to the reference (see Table 6 page 21) The pyrazole and triazole nucleus substituted by the chlorine atom (–Cl) increased the activity. In addition, the substitution of pyrazole nucleus by chlorophenyl/Fluorophenyl leads to the decrease of the activity. The development of a pyrazolo pyrimidine series showed

Table 15: Mean Zone of Inhibition beyond Well Diameter (6 mm) produced on a Range of Clinically Pathogenic Microorganisms using a 5 mg/ml Concentration of Tested Samples

Compounds	Fungi		Gram-Positive Bacteria		Gram-Negative Bacteria	
	A.fumigatus	*C.albicans*	*S. pneumonia*	*B.subtilis*	*P. aeruginosa*	*E. coli*
(96)	12.6	11.2	0	0	0	0
(97)	17.3	16.9	17.3	18.3	18.3	22.6
(98)	21.2	19.6	23.8	23.8	17.3	19.9
(99)	20.8	16.8	13.1	10.8	13.4	12.3
(100)	26.8	15.3	11.2	12.7	9.8	11.3
(101)	20.6	15.8	18.9	12.7	11.3	9.9
(102)	23.8	32.4	13.2	13.3	0	10.2
Amphotericin B	23.7	25.4	–	–	–	–
Ampicillin	–	–	23.8	32.4	–	–
Gentamicin	–	–	–	–	17.3	19.9

that compound 46 (Figure 7) has high antibacterial activity on *B. Subtilis*. Subsequently, a series of pyrazole azitidinone was studied. Compound 54 (Figure 8) showed high antibacterial activity due to the fact that the pyrazole ring substituted with fluoro, chloro, bromophenyl and phenylacetyl increases the antimicrobial activity, while compounds 55 and 56 showed moderate activity. Then, a new series based on pyrazole carboxamide presented compounds 57, 58 and 59 (Figure 9) having the donor substituents and electron-withdrawers, Chloro, N-dimethyl of the phenyl ring. This gives excellent activity with inhibition of *S. aureus* respectively. Morever, conjugates 70, 72

Table 16 : Concentration Minimale Inhibitrice (µg/mL) des Composés(103-111) Synthétisés les plus Puissants Contre les Organismes Pathologiques

Compounds	Gram + bacteria				Gram – bacteria		Fungi		
	S. Aureus	*S. epidermidis*	*B. subtilis*	*P. vulgaris*	*K. pneumonia*	*S. flexneri*	*A. fumigates*	*A. clavatus*	*C. albicans*
(103)	0.97	0.97	1.95	0.97	1.95	1.95	7.81	15.63	1.95
(104)	0.24	0.24	0.06	9.9	3.9	0.48	1.95	3.9	0.48
(105)	3.9	3.9	1.97	7.81	3.9	7.81	7.81	15.63	7.81
(106)	0.97	3.9	0.97	3.9	3.9	3.9	15.63	7.81	3.9
(107)	1.95	0.98	0.49	31.25	7.81	7.81	0.98	7.81	0.49
(108)	3.9	0.98	0.98	500	31.25	31.25	15.63	7.8	1.95
(109)	1.95	15.63	1.95	125	31.25	15.63	31.25	3.9	1.95
(110)	–	–	–	–	–	–	7.81	7.81	1.95
(111)	0.49	0.49	0.12	0.98	0.49	0.12	0.98	0.49	0.12
Ampicillin	0.06	0.48	0.007	–	–	–	–	–	–
Gentamycin	–	–	–	1.95	0.24	0.48	–	–	–
Amphotericin	–	–	–	–	–	–	0.97	1.95	0.48

S. aureus/ S. epidermidis/ B. subtilis/ P. vulgaris/ K. pneumonia/ S. flexneri/ A. fumigatus/ A. clavatus/ C. albicans.

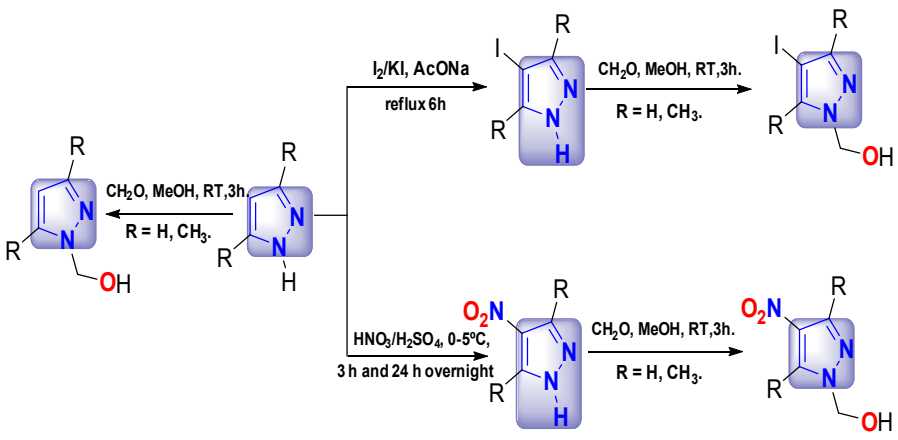
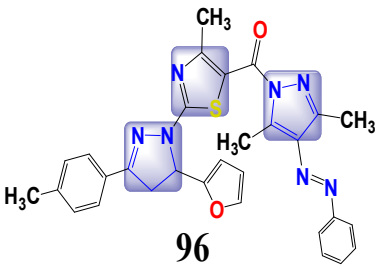


Fig. 18: The Alkylaminopyrazole Derivatives substituted Aminohexadecan

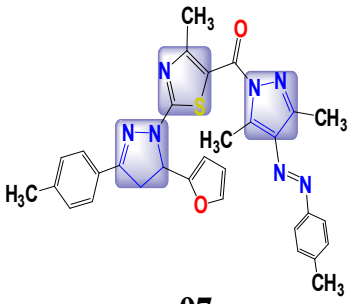
and 75 (Figure 11) showed promising antimicrobial results. This may be explained by the presence of an electron-withdrawing group with the benzene ring, whereas the 73 and 74 (Figure 13) conjugates had no effect on all bacterial strains.

More so, a series of thiazole-based pyrazole was tested for their antimicrobial activity. The studied compounds are not active against antifungal activity, while the derivative 77 (Figure 13) exerted the most significant antimicrobial activity against Proteus vulgaris (MIC=312.5 µg/mL). This is explained by the pyrazole ring substituted with –NH2 at position 5



96

(*E*)-(3,5-dimethyl-4-(phenyldiazenyl)-1*H*-pyrazol-1-yl)(2-(5-(furan-2-yl)-3-(*p*-tolyl)-4,5-dihydro-1*H*-pyrazol-1-yl)-4-methylthiazol-5-yl)methanone



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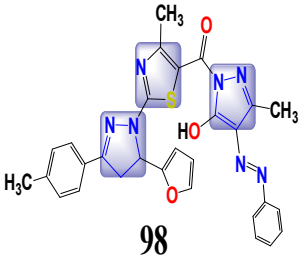
(*E*)-(3,5-dimethyl-4-(*p*-tolyldiazenyl)-1*H*-pyrazol-1-yl)(2-(5-(furan-2-yl)-3-(*p*-tolyl)-4,5-dihydro-1*H*-pyrazol-1-yl)-4-methylthiazol-5-yl)methanone



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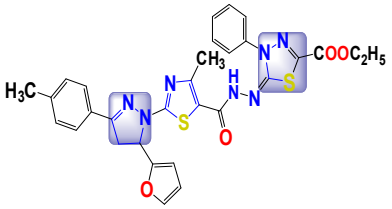
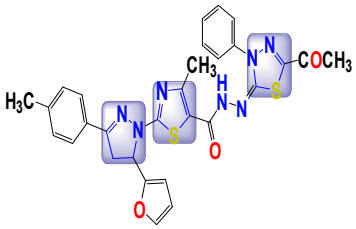
(*E*)-(2-(5-(furan-2-yl)-3-(*p*-tolyl)-4,5-dihydro-1*H*-pyrazol-1-yl)-4methylthiazol-5-yl)(5-hydroxy-3-methyl4 (phenyldiazenyl) -1*H*-pyrazol-1-yl)methanone



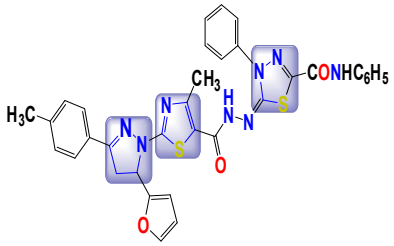
99

ethyl (*E*)-5-(2-(2-(5-(furan-2-yl)-3-(*p*-tolyl)-4,5-dihydro-1*H*-pyrazol-1-yl)-4-methylthiazole-5-carbonyl)hydrazono)-4-phenyl-4,5-dihydro-1,3,4-thiadiazole-2-carboxylate



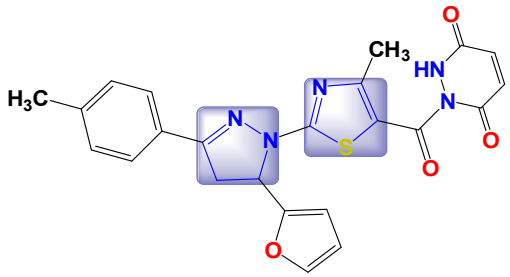
100

(*E*)-*N*'-(5-acetyl-3-phenyl-1,3,4-thiadiazol-2(3*H*)-ylidene)-2-(5-(furan-2-yl)-3-(*p*-tolyl)-4,5-dihydro-1*H*-pyrazol-1-yl)-4-methylthiazole-5-carbohydrazide



101

(*E*)-5-(2-(2-(5-(furan-2-yl)-3-(*p*-tolyl)-4,5-dihydro-1*H*-pyrazol-1-yl)-4-methylthiazole-5-carbonyl)hydrazono)-*N*,4-diphenyl-4,5-dihydro-1,3,4-thiadiazole-2-carboxamide



102

1-(2-(5-(furan-2-yl)-3-(*p*-tolyl)-4,5-dihydro-1*H*-pyrazol-1-yl)-4-methylthiazole-5-carbonyl)-1,2-dihydropyridazine-3,6-dione

Fig. 19: Pyrazole-1-Carbothioamide Derivative Structures versus Blue Colored and Red Colored Bacteria.

and phenyl at position 4 increases activity. Then, molecule 91 (Figure 18) based on alkylamino pyrazole presented the highest activity against Bacillus subtilis (MIC=0.007 µg/mL). This results from an iodine (I) atom in position 4 of the pyrazole ring. Other carbothioamide-based pyrazole derivatives were studied. This family showed that compound 96 (Figure 19) has high antimicrobial and antifungal activity. The pyrazole ring substituted with electron-donating groups like methyl and furan increases the activity of this compound. Also, another family of quinoline-based pyrazole showed that the derivative 104 is a more potent MIC compared to the standard, against S. epidermidis, and similar to the standard against S. flexneri, and C. albicans. Moreover, compounds 115, 114 (Figure 21) showed inhibited activities compared to all conjugates. These results showed that the other larger substituents reduce the antibacterial activity. Furthermore, the coumarin present in the plant showed that compounds 129 and 131 (Figure 24) presented an improved antibacterial activity compared to the other compounds. Vis-à-vis *Escherichia coli,* when the R1 position was substituted by other entities, the antibacterial activity was higher; and when R1 represents chlorine (–Cl), 131, it generates an excellent MIC value.

In the light of these results, we remarked that chitosan-based pyrazole, thiophene-attached carboxamide pyrazoles, pyrazoline and pyrazolone showed significant antimicrobial and antifungal activity. These families of pyrazoles can be considered as a lead for researchers to develop other series of pyrazoles with remarkable biological activity.

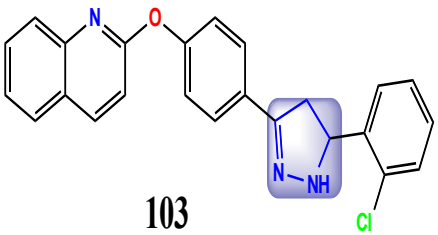
According to the discussion and comparison made on the different pyrazole families, we can say that the present pyrazole is a candidate for the researchers, due to the chemical property of pyrazole core. Also, the results prompted the authors to continue the research in order to establish a thorough experimental study.

CONCLUSION

There is increasing encourage in the

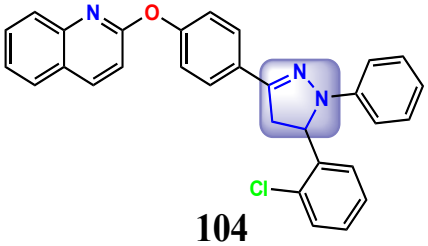
Table 17: Antimicrobial Activities of the Synthesized Compounds against the Pathological Organisms expressed as Inhibition Diameter Zones in Millimeters

Compounds	Gram Positive Bacteria			Gram Negative-Bacteria		Fungi		
	B. subtilis	*S. pneumonia*	*E. coli*	*P. aeruginosa*	*A. fumigatus*	*C.albicans*	*S. strumracemosum*	*G. candidum*
(112)	19.3±0.19	17.8±0.44	NA	16.7±0.58	NA	16.8±0.58	18.7±0.44	20.6±0.19
(113)	20.3±0.5	17.9±0.63	NA	18.7±0.19	NA	14.8±0.19	17.8±0.63	19.3±0.44
(114)	18.9±0.25	16.8±0.19	NA	18.3±0.25	NA	14.9±0.58	17.2±0.37	18.7±0.37
(115)	18.7±0.25	16.2±0.58	NA	17.3±0.44	NA	14.8±0.37	16.3±0.25	18.8±0.44
(116)	14.9±0.25	11.7±0.37	NA	13.4±0.37	NA	11.4±0.25	11.7±0.19	12.9±0.19
(117)	23.4±0.37	19.1±0.25	NA	20.9±0.58	NA	17.8±0.25	21.9±0.25	29.8±0.19
Amphotericin	25.4±0.1	28.7±0.2	19.7±0.2	23.7±0.1	–	–	–	–
Ampicilline	–	–	–	–	–	–	23.8±0.2	32.4±0.3
Gentamicin	–	–	–	–	17.3±0.1	19.9±0.3	–	–



103

2-(4-(5-(2-chlorophenyl)-4,5-dihydro-1*H*-pyrazol-3-yl)phenoxy)quinoline



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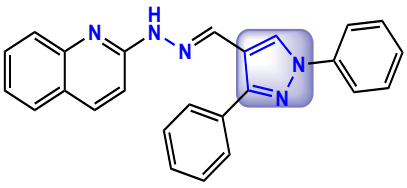
2-(4-(5-(2-chlorophenyl)-1-phenyl-4,5-dihydro-1*H*-pyrazol-3-yl)phenoxy)quinoline



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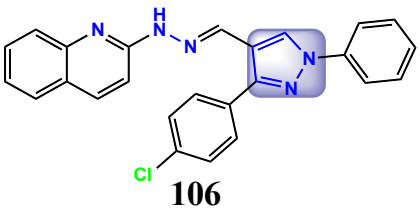
(*E*)-2-(2-((1,3-diphenyl-1*H*-pyrazol-4-yl)methylene)hydrazinyl)quinoline



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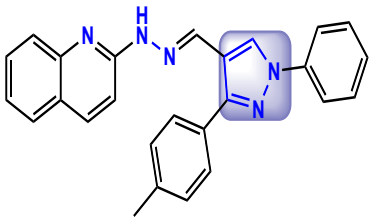
(*E*)-2-(2-((3-(4-chlorophenyl)-1-phenyl-1*H*-pyrazol-4-yl)methylene)hydrazinyl)quinoline



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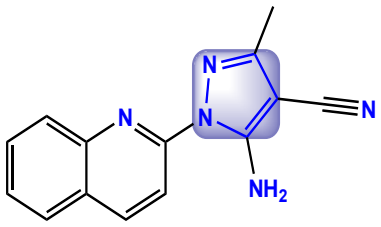
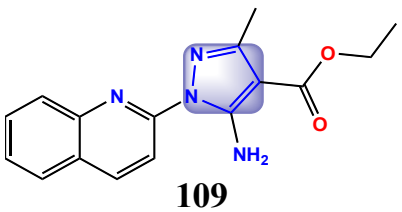
(*E*)-2-(2-((1-phenyl-3-(*p*-tolyl)-1*H*-pyrazol-4-yl)methylene)hydrazinyl)quinoline



108

5-amino-3-methyl-1-(quinolin-2-yl)-1*H*-pyrazole-4-carbonitrile



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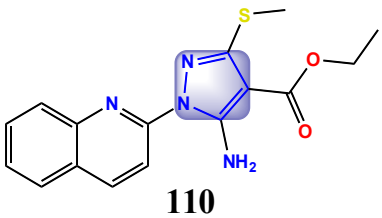
ethyl 5-amino-3-methyl-1-(quinolin-2-yl)-1*H*-pyrazole-4-carboxylate

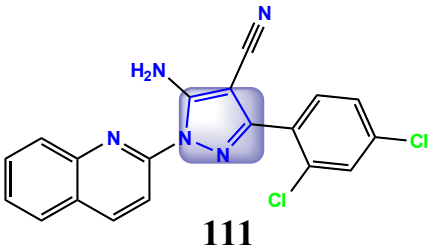


110

ethyl 5-amino-3-(methylthio)-1-(quinolin-2-yl)-1*H*-pyrazole-4-carboxylate

evolution of bioactive molecules wearing the heterocyclic pyrazole. This critical investigation sheds light on how to design and create new drugs from pyrazole derivatives versus bacteria and fungi. We have illustrated the latest structures with recently published antimicrobial potential to help better understand this category of compounds and applications of this family versus blue-colored bacteria, red-colored bacteria and fungi have promising results. Then, we have examined more than 134 pyrazole derivatives and can draw the following conclusions:

1. A new basic schiff series has been reported by the reaction of chitosan with different substituted pyrazole-4-carbaldehydes. The results showed a good antimicrobial property compared to the chitosan of the mother fraction.
2. In this study, we have highlighted a new ecological strategy for the synthesis of pyrazole carboxamides attached to thiophene. The attendance of N, N-dimethyl, chloro substitutions, an aromatic cycle, is considered the characteristic of the antimicrobial potency of the synthesized compounds.
3. Pyrazole carrying pyrazoline derivatives could be synthesized using both microwave and conventional methods.
4. Pyrazole, pyrazolone and enaminonitrile pyrazole derivatives:
   - Their antimicrobial activities were very hopeful.
   - The effectiveness of the compounds depends on radical position.



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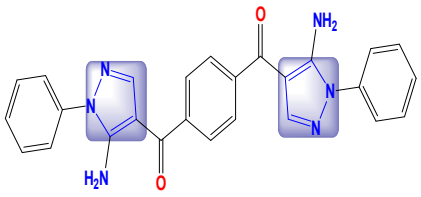
5-amino-3-(2,4-dichlorophenyl)-1-(quinolin-2-yl)-1*H*-pyrazole-4-carbonitrile



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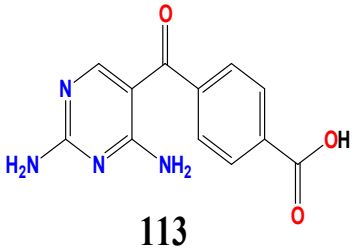
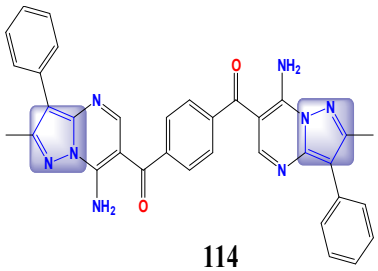
1,4-phenylenebis((5-amino-1-phenyl-1*H*-pyrazol-4-yl)methanone)



113

4-(2,4-diaminopyrimidine-5-carbonyl)benzoic acid



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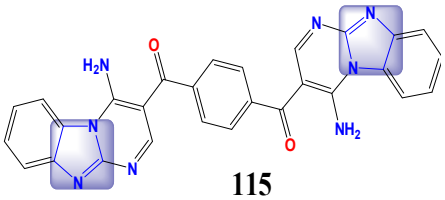
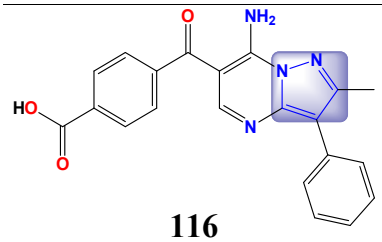
1,4-phenylenebis((7-amino-2-methyl-3-phenylpyrazolo[1,5-*a*]pyrimidin-6-yl)methanone)



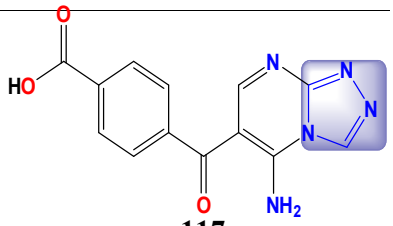
115

1,4-phenylenebis((4-aminobenzo[4,5]imidazo[1,2-*a*]pyrimidin-3-yl)methanone)



116

4-(7-amino-2-methyl-3-phenylpyrazolo[1,5-*a*]pyrimidine-6-carbonyl)benzoic acid



117

4-(5-amino-[1,2,4]triazolo[4,3-*a*]pyrimidine-6-carbonyl)benzoic acid

Fig. 21: Structure of Pyrazole and Pyrimidine Derivatives versus Blue Colored and Red Colored Bacteria.

Table 18: Minimum Inhibitory Concentration (MIC) Determination

Compounds	MIC (µg/mL)			
	E. coli	*S. aureus*	*B. subtilis*	*C. albicans*
(118)	62.5	–	31.25	–
(119)	–	125	–	62.5
(120)	125	125	31.25	–
(121)	31.5	62.5	>125	–
(122)	62.5	>125	–	>125
Ciprofloxacin	3.95	2	2	–
Fluconazole	–	–	–	2
Fluconazole	–	–	–	2

5. The synthesis of a new series of pyranopyrazole shows exceptional antimicrobial activity and the presence of a substituent Nitro ($-NO_2$) electron attractor can, without any doubt, improve the activity.
   - In addition, compounds 70, 72 and 75 have shown promising results of antimicrobials. This may be justified through the attendance of an electron-attracting radical attached to the benzene ring, while combinations 73 and 74 had no effect on all bacterial strains.

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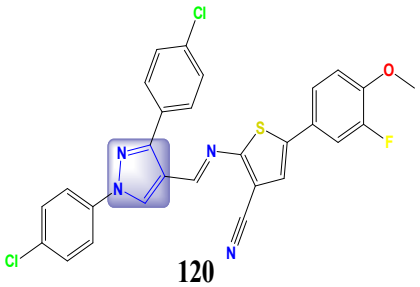
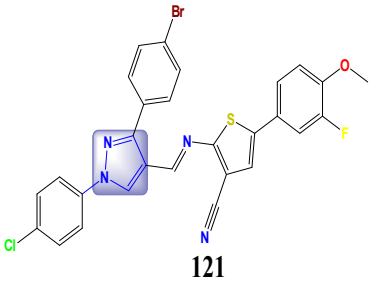


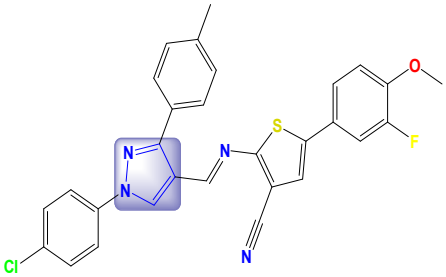
120

(*E*)-2-(((1,3-bis(4-chlorophenyl)-1 *H*-pyrazol-4-yl)methylene)amino) -5-(3-fluoro-4-methoxyphenyl)thiophene-3-carbonitrile



121

(*E*)-2-(((3-(4-bromophenyl)-1-(4-chlorophenyl)-1*H*-pyrazol-4-yl)methylene)amino)-5-(3-fluoro-4-methoxyphenyl)thiophene -3-carbonitrile



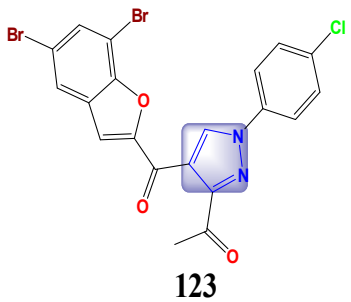
122

(*E*)-2-(((1-(4-chlorophenyl)-3-(*p*-tolyl)-1*H*-pyrazol-4-yl)methylene) amino)-5-(3-fluoro-4-methoxyphenyl)thiophene-3-carbonitrile

Fig. 22: Structures of Pyrazole-4-Carboxaldehyde Derivatives versus Blue Colored and Red Colored Bacteria.

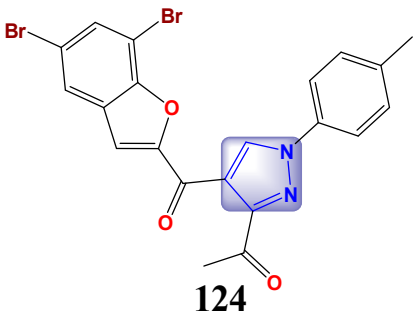
Table 19: MIC (µg/ml) of the Antibacterial Synthesized Pyrazoles

Compounds	Minimum Inhibitory Concentration (µg/mL)			
	Gram-positive Bacteria		Gram-negative Bacteria	
	S. aureus	*S. mutans*	*E. coli*	*K. pneumonia*
(123)	–ve	1000	–ve	–ve
(124)	7.8	15.6	15.6	3.9
(125)	–ve	500	–ve	–ve
(126)	–ve	–ve	1000	–ve
(127)	–ve	1000	–ve	–ve
(128)	–	–	31.25	62.5
Gentamicin	62.5	62.5	–	–
Ampicillin				



123

1-(1-(4-chlorophenyl)-4-(5,7-dibromobenzofuran -2-carbonyl)-1*H*-pyrazol-3-yl)ethan-1-one



124

1-(4-(5,7-dibromobenzofuran-2-carbonyl)-1-(*p*-tolyl)-1*H*-pyrazol-3-yl)ethan-1-one

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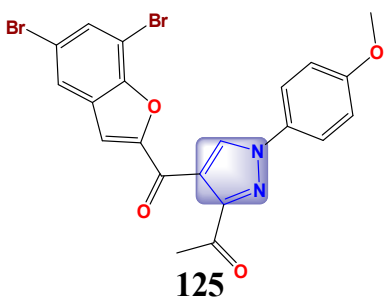
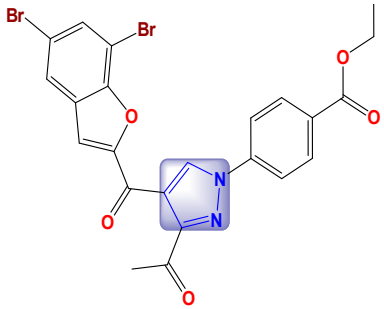


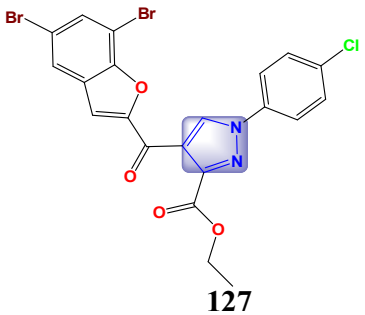
125

1-(4-(5,7-dibromobenzofuran-2-carbonyl)-1-(4-methoxyphenyl)-1*H*-pyrazol-3-yl)ethan-1-one



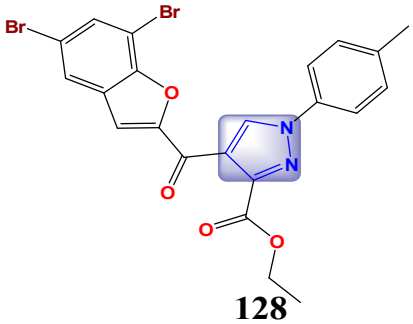
126

ethyl 4-(3-acetyl-4-(5,7-dibromobenzofuran-2-carbonyl)-1*H*-pyrazol-1-yl)benzoate



127

ethyl 1-(4-chlorophenyl)-4-(5,7-dibromobenzofuran-2-carbonyl)-1*H*-pyrazole-3-carboxylate



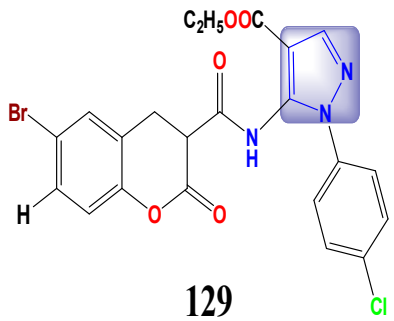
128

ethyl 4-(5,7-dibromobenzofuran-2-carbonyl)-1-(*p*-tolyl)-1*H*-pyrazole-3-carboxylate

Fig. 23. Pyrazole-benzofuranhybrid Derivative Structures versus Blue Colored and Red Colored Bacteria

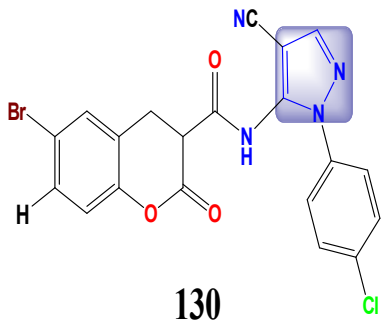
Table 20: Chemical Structures of Compounds (129–134) and MIC values versus *S. aureus*, *L. monocytogenes*, *E. coli* and *Salmonella*.

Compounds	MIC (mg/L)			
	S. aureus	*L. monocytogenes*	*E. coli*	*Salmonella*
(129)	4	1	8	32
(130)	4	16	8	0.25
(131)	0.5	0.5	0.25	4
(132)	16	8	4	0.125
(133)	1	0.5	2	0.05
(134)	2	2	4	0.125
CIP[b]	0.125	1	0.5	0.25
NB[c]	2	0.25	4	0.5



129

ethyl 5-(6-bromo-2-oxochromane-3-carboxamido)-1-(4-chlorophenyl)-1*H*-pyrazole-4-carboxylate



130

6-bromo-*N*-(1-(4-chlorophenyl)-4-cyano-1*H*-pyrazol-5-yl)-2-oxochromane-3-carboxamide

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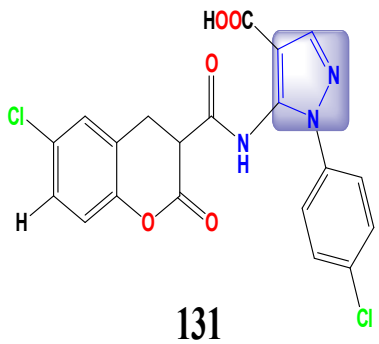
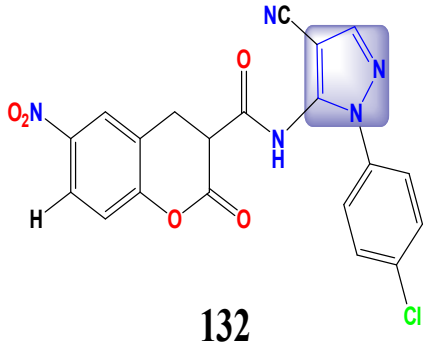


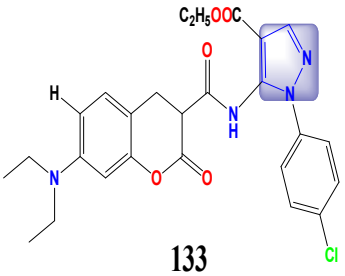
131

5-(6-chloro-2-oxochromane-3-carboxamido)
-1-(4-chlorophenyl)-1*H*-pyrazole-4-carboxylic acid



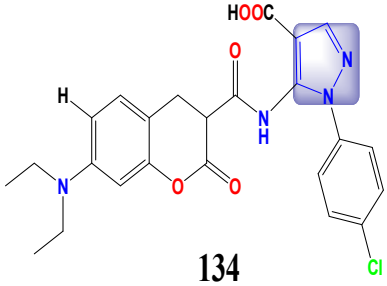
132

N-(1-(4-chlorophenyl)-4-cyano-1*H*-pyrazol-5-yl)
-6-nitro-2-oxochromane-3-carboxamide



133

ethyl 1-(4-chlorophenyl)-5-(7-(diethylamino)-2-oxochromane
-3-carboxamido)-1*H*-pyrazole-4-carboxylate



134

1-(4-chlorophenyl)-5-(7-(diethylamino)-2-oxochromane-3-
carboxamido)-1*H*-pyrazole-4-carboxylic acid

Fig. 24: Structures of Coumarin-Pyrazole Carboxamide Derivatives versus Blue Colored and Red Colored Bacteria