PYRAZOLONE: A NEW PROFILE OF BIOLOGICAL ACTIVITIES AND SYNTHESIS

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Summary

Pyrazolone, a five-membered-ring lactam, is a derivative of pyrazole that has an additional keto (=O) group have been studied extensively owing to their interesting pharmacological activities. This review article covers the most active Pyrazolone derivatives that have shown considerable biological actions such as antimicrobial, anti-inflammatory, anticancer, antilipidemic, antiviral, antihypertensive, and antitubercular. This review also discusses the structure-activity relationship of the most potent compounds. It can act as an important tool for medicinal chemists to develop newer compounds possessing Pyrazolone moiety that could be better agents in terms of efficacy and safety.

Keywords: Biological activities, pyrazolone, SAR, Total synthesis.

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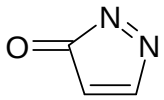
Introduction

Pyrazolone, a five-membered-ring lactam, is a derivative of pyrazole that has an additional keto (=O) group. It has a molecular formula of $C_3H_4N_2O$.

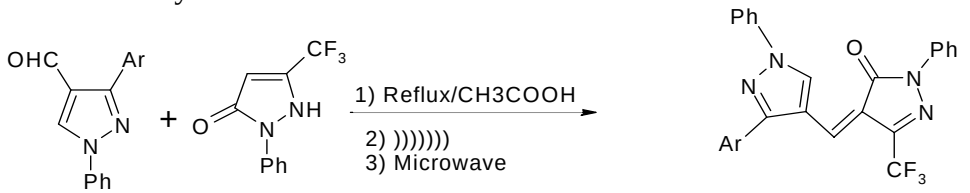


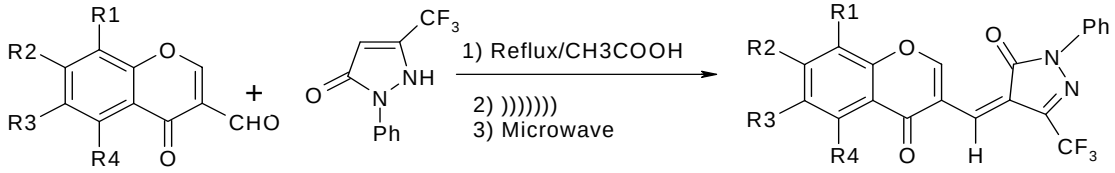
Examples of derivatives include:

- Ampyrone
- Metamizole
- Phenazone
- Phenylbutazone

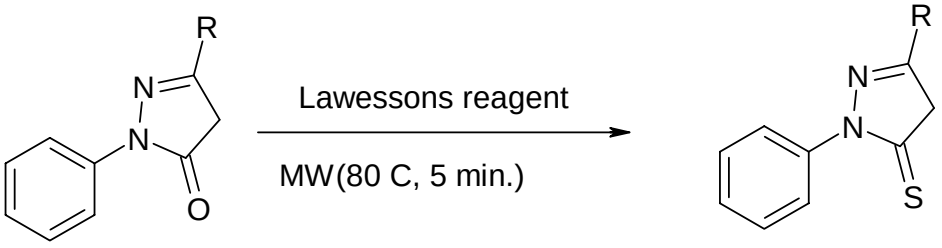
Antimicrobial Activity:

1. Various Fluorine containing pyrazolone derivatives have been synthesized by conventional and non-conventional methods and screened for antimicrobial activity. [1]



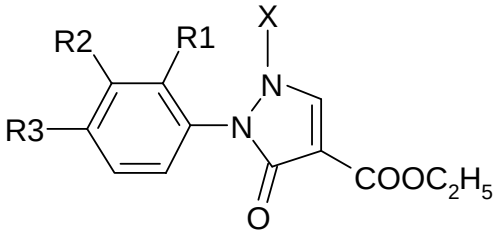


2. 2-Pyrazoline-5-ones and 2-pyrazoline-5-thiones as active Michael donors for the synthesis of novel spirocyclohexanone derivatives were prepared and screened for antimicrobial activity against *S.Typhi, S.aures* and *E.coli* bacteria. [2]



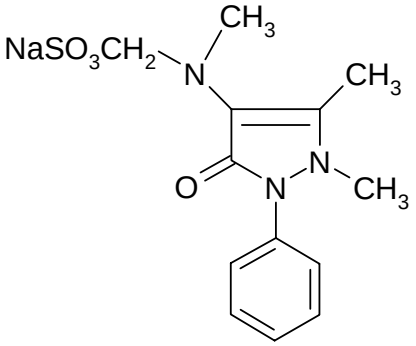
Hypoglycemic Activity

Several new aryl substituted pyrazol-3-one derivatives were prepared by reaction of substituted phenyl hydrazine with diethylethoxymethelyne malonate and were screened for hypoglycemic activity with standard drug Metformin.[3]

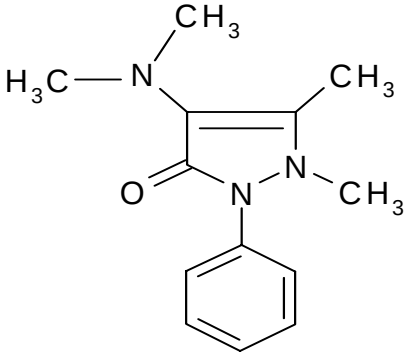


Human neutrophils oxidative burst inhibitors

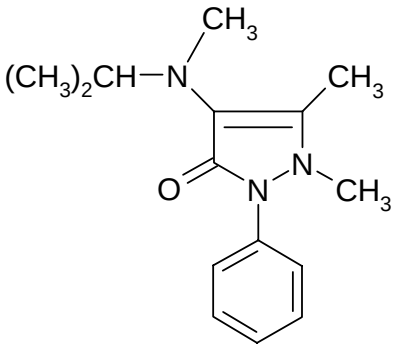
The aim of the present study was to evaluate the putative inhibitory effect of the pyrazolones dipyrone, aminopyrine, isopropylantipyrine, and antipyrine against human neutrophil burst and their scavenging activity against O2 S_, H2O2, HOS, ROOS, and HOCl. The obtained results showed that dipyrone and aminopyrine prevent phorbol-12-myristate-13-acetate-induced neutrophil burst with high efficiency.[4]



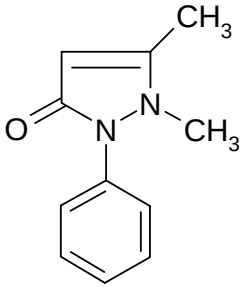
Dipyrone



Aminopyrine



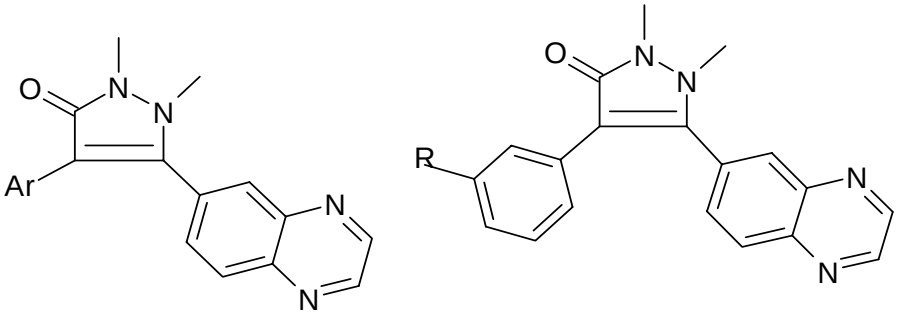
Isopropyl aminopyrie



Antipyrine

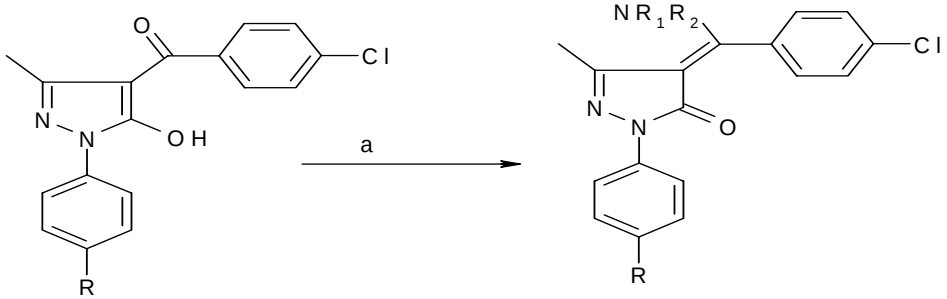
Pyrazolone based TGFβR1 kinase inhibitor

Interruption of TGFb signaling through inhibition of the TGFbR1 kinase domain may prove to have beneficial effect in both fibrotic and oncological diseases. Herein we describe the SAR of a novel series of TGFbR1 kinase inhibitors containing a pyrazolone core. Most TGFbR1 kinase inhibitors described to date contain a core five-membered ring bearing N as H-bond acceptor. Described herein is a novel strategy to replace the core structure with pyrazolone ring, in which the carbonyl group is designed as an H-bond acceptor to interact with catalytic Lys 232.[5]



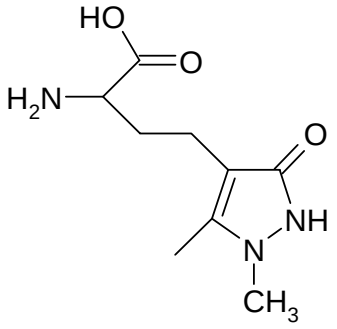
Anti tubercular

Two series of novel rigid pyrazolone derivatives were synthesized and evaluated as inhibitors of Mycobacterium tuberculosis (MTB), the causative agent of tuberculosis. Two of these compounds showed a high activity against MTB (MIC = 4 lg/mL). The newly synthesized pyrazolones were also computationally investigated to analyze if their properties fit the pharmacophoric model for antitubercular compounds previously built by us. The results are in agreement with those reported by us previously for a class of pyrazole analogues and confirm the fundamental role of the p-chlorophenyl moiety at C4 in the antimycobacterial activity. [6]



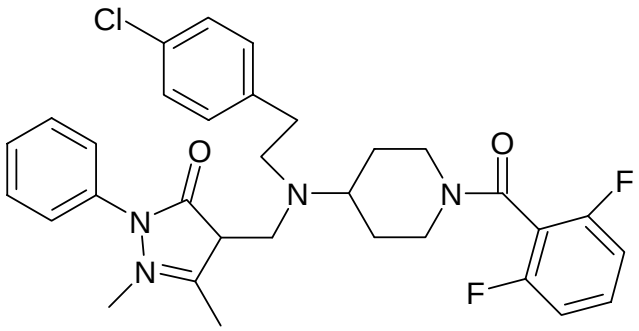
CNS Antidepressant activity

The higher homologue of (*S*)-glutamic acid [(*S*)-Glu], (*S*)-á-aminoadipic acid [(*S*)-á-AA] is selectively recognized by the mGlu2 and mGlu6 subtypes of the family of metabotropic glutamic acid (mGlu) receptors. Furthermore, a number of analogues of (*S*)-á-AA, in which the terminal carboxyl group has been replaced by various bioisosteric groups, such as phosphonic acid or 3-isoxazolol groups, have been shown to interact selectively with different subtypes of mGlu receptors. In this paper we report the synthesis of the 3-pyrazolone bioisosteres of á-AA, compounds (*RS*)-2-amino-4-(1,2-dihydro-5-methyl-3-oxo-3*H*-pyrazol-4-yl)butyric acid (**1**) and (*RS*)-2-amino-4-(1,2-dihydro-1,5-dimethyl-3-oxo-3*H*-pyrazol-4-yl)butyric acid.[7]



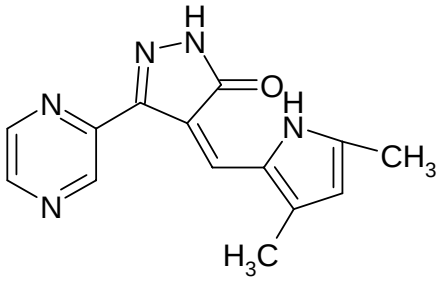
CCR3 antagonist

The discovery and optimization of a novel class of potent CCR3 antagonists is described. Details of synthesis and SAR are given together with some ADME properties of selected compounds. An optimal balance between activities, physicochemical properties, and in vitro metabolic stability was reached by the proper choice of substituents.[8]



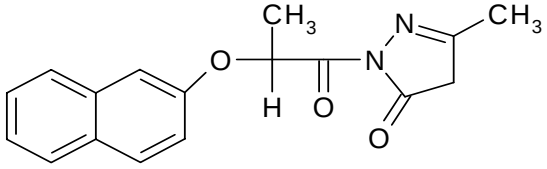
Anti-Angiogenic Activity

Structural analysis of the essential binding elements of the oxindole-based kinase inhibitor (1) led to the identification of a novel class of heterocyclic-substituted pyrazolones. Knoevenagel condensation of a variety of activated methylene nucleophiles with indole or pyrrole carboxaldehydes provided a focused library of molecules, each containing elements of kinase pharmacophore probe. Initial screening for VEGFR-2 kinase inhibition eliminated several of the probes. Identification of an active pyrazolone motif and further optimization resulted in several highly potent VEGFR-2 inhibitors with cellular efficacy, anti-angiogenic activity ex vivo in rat aortic ring explant cultures, and oral anti-tumor efficacy in nude mice.[9]



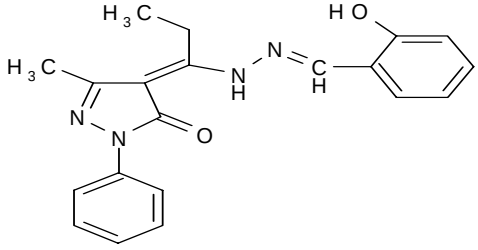
Hypolipidemic Activity

A series of 2-(naphthalen-2-yloxy)propionic acid derivatives were prepared. The hypolipidemic activity of the new compounds as well as the intermediate acid 2 was evaluated in the high cholesterol diet (HCD) fed hyperlipidemic rat model. Interestingly, the S-alkylated mercaptotriazole and the 1,3,4-oxadiazole produced striking reduction of serum levels of total cholesterol (TC), triglycerides (TGs) and low-density lipoproteins (LDLs) and elevation of serum high-density lipoproteins (HDLs) being more active than the reference gemfibrozil. In addition, the 1,2,4-triazole 7a, the hydroxypyrazoline and the pyrazolone derivative exhibited good hypolipidemic activity on different lipid parameters.[10]

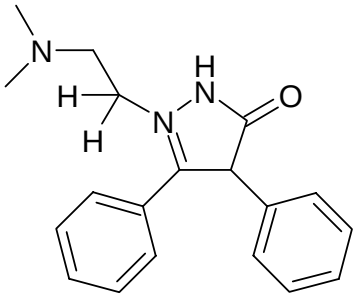


Anticancer activity

1. The pyrazolone derivative N-(1-phenyl-3-methyl-4-propyl-pyrazolone-5)-salicylidene hydrazone (H2L) and its copper(II) complex [Cu2L2CH3OH]_2CH3OH have been both synthesized and characterized by elemental analyses, IR spectroscopy, X-ray crystallography, theoretical calculation and pharmacological testing. It's found that the Cu(II) complex possesses more powerful anticancer effectivity than that of the ligand. In order to make its anticancer principium clearly, we investigate their structures. In ligand there are several coordination spots, such as N, O atoms, which are close to biological environment. The crystallographic structural analysis of the complex reveals that the two Cu centers display two different coordination patterns. O1, O2, N3, and N4 from the ligand take part in the coordination with Cu atoms, resulting in the formation of the double-nuclear complex. The pharmacological testing results show that the coordination effect improves the antitumor activity of the ligand. The calculated Fukui function for H2L and its deprotonated form L2_ predicts that the most probable reactive sites for electrophilic attack are oxygen atoms.[11]

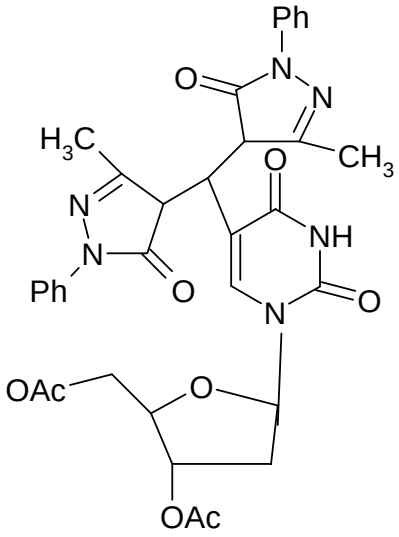


2. New compounds, structurally related to the potent protein kinase C inhibitor staurosporine, with a bisindolylpyrazolone framework and substituted on the pyrazolone nitrogens with N,N-dialkylaminoalkyl side chain, were synthesized and evaluated for growth-inhibitory properties in several human cell lines. Many showed inhibition of TNF-a production in response to the tumor promotor TPA on HL-60 cells. The apoptotic activity on HeLa cells has been examined for several of these compounds.[12]



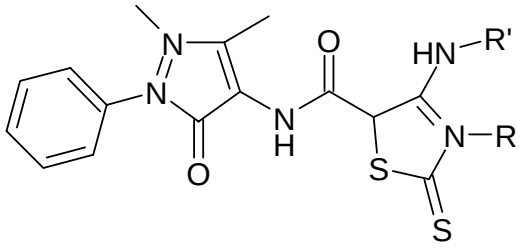
Anti-Orthopoxvirus Activity

Synthetic hybridization of two privileged drug scaffolds, pyrazolone on the one hand and pyrimidine nucleoside on the other, resulted in the generation of two novel 5-substituted pyrimidine nucleosides with potent in vitro antiviral activity against two representative orthopoxviruses, vaccinia virus and cowpox virus.[13]



Anti-Inflammatory activity

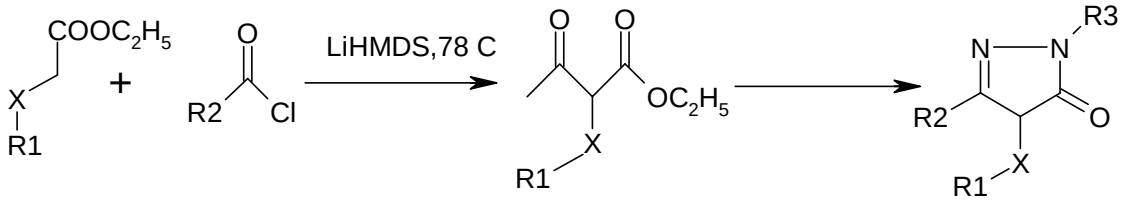
The synthesis of two groups of structure hybrids comprising basically the antipyrine moiety attached to either polysubstituted thiazole or 2,5-disubstituted-1,3,4-thiadiazole counterparts through various linkages is described. Twelve out of the newly synthesized compounds were evaluated for their anti-inflammatory activity using two different screening protocols; namely, the formalin-induced paw edema and the turpentine oil-induced granuloma pouch bioassays, using diclofenac Na as a reference standard. The ulcerogenic effects and acute toxicity (ALD50) values of these compounds were also determined. Meanwhile, the analgesic activity of the same compounds was evaluated using the rat tail withdrawal technique. Additionally, the synthesized compounds were evaluated for their in vitro antimicrobial activity. In general, compounds belonging to the thiazolylantipyrine series exhibited better biological activities than their thiadiazolyl structure variants. compounds proved to display distinctive anti-inflammatory and analgesic profiles with a fast onset of action. All of the tested compounds revealed super GI safety profile and are well tolerated by the experimental animals with high safety margin (ALD50 > 3.0 g/kg).[14]



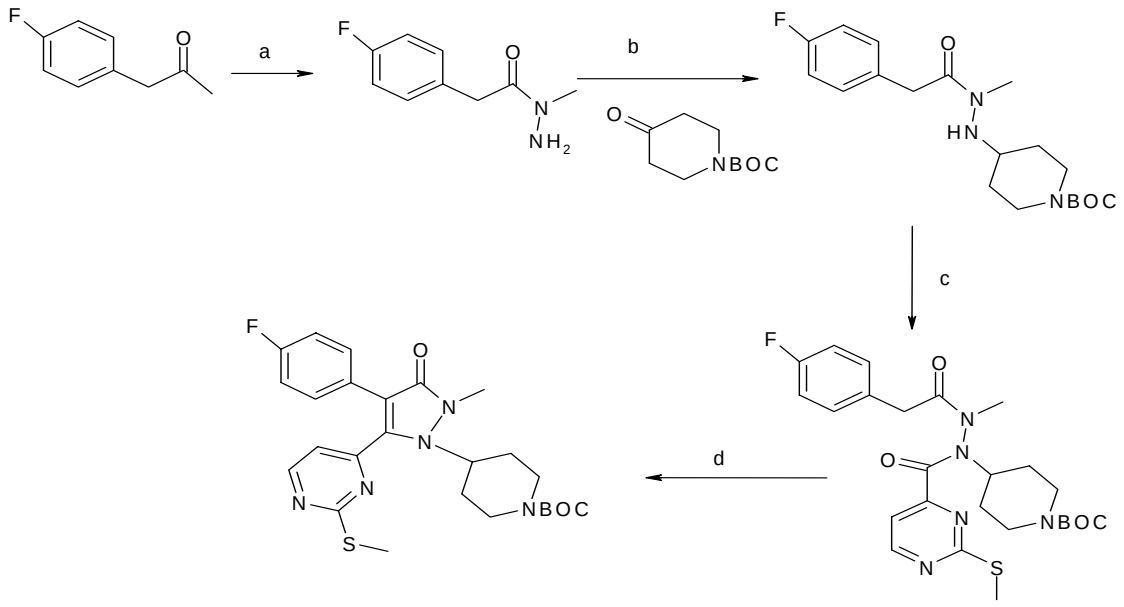
Method of synthesis

1. **Cross claisen condensation**

a-Oxy/thio substituted-b-keto esters were synthesized through an efficient cross-Claisen condensation of aryl oxy/thio acetic acid ethyl esters with acid chlorides, then it is converted in situ into 4-oxy/thio substituted-1H-pyrazol-5(4H)-ones by the addition of hydrazine or hydrazine derivatives and screened for their antibacterial, antifungal activities.[15]

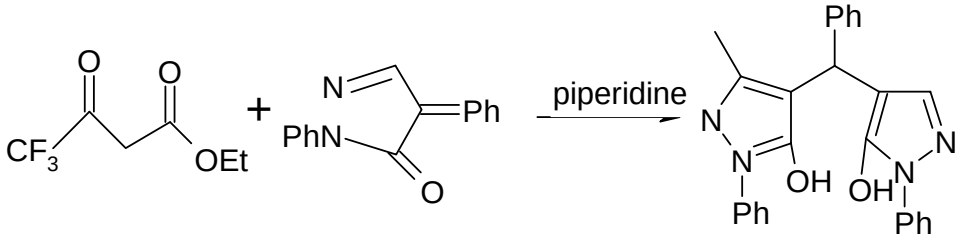


2. Cyclization of various bisacylated hydrazines and pyrazolidines using DBU or sodium hydride leads to the formation of various mono-, bi- and tricyclic pyrazolone scaffolds in 41–98% yield. The convergent nature by which the precyclization intermediates are constructed allows for rapid derivatization about the pyrazolone core.[16]



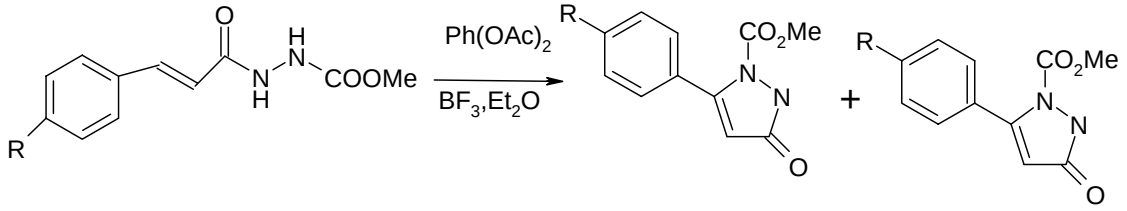
Regioselective synthesis of 6-trifluoromethyl-1, 4, 5, 6-tetrahydropyrazolo [3, 4-b] pyran.

3. A facile two-step procedure for the synthesis of 6-(trifluoromethyl)-1,4,5,6-tetrahydropyrazolo[3,4-b]pyran derivatives (4) from the reaction of 4-arylidene-3-methyl-1-phenyl-5-pyrazolones (1) with ethyl trifluoroacetoacetate (2), a versatile fluorinated building-block, was presented.Furthermore, to increase the efficiency of this reaction, the more convenient one-pot three-component process was also developed with a slightly lower yield. Treatment of 4 with P2O5, conc. H2SO4, POCl3/Py or p-TsOH under the drastic conditions did not afford the corresponding dehydrated products.[17]



A simple approach to pyrazol-3-ones via diazenes

4. An efficient entry into pyrazol-3-ones is described starting from propenoic acids that were first transformed into the corresponding hydrazides. Oxidation of the hydrazides gave the diazenes and the latter cyclized to pyrazol-3-ones on treatment with ZrCl4. The methoxycarbonyl protection of the N-1 of the pyrazolone derivatives was easily removed under mild reaction conditions.[18]



Conclusion

The plethora of research subscribed in this review indicates a wide spectrum of pharmacological activities exhibited by pyrazolone derivatives. The biological profiles of these new generations of pyrazolone would represent a fruitful matrix for further development of better medicinal agents.

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