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A review on recent advances for the synthesis of bioactive pyrazolinone and pyrazolidinedione derivatives

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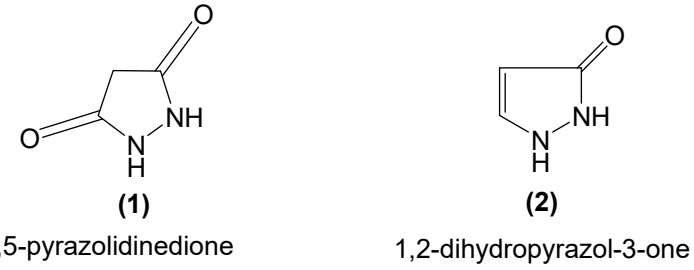
Oxo derivatives of pyrazolines and pyrazolidines are important heterocyclic compounds due to their unique biological activities and have been widely applied in pharmaceutical and agromedical fields. In this review, we provide an account of some recent advances in the field of pyrazolone chemistry, specifically on the reported synthesis methods of pyrazolinone (3-oxo-1,2-dihydropyrazole) and 3,5-pyrzolidinediones (3,5-dioxotetrahydropyrazoles) derivatives.

1. Introduction

The heterocyclic compounds involving pyrazolinone (3-oxo-1,2-dihydropyrazole) and 3,5-pyrzolidinediones (3,5-dioxotetrahydropyrazoles) were reported for their wide range of pharmacological and agricultural activities.[1-5] The incorporation of an active scaffold in the structure of heterocyclic compounds enhances properties associated with them. This has proven useful in the development of newer effective heterocycles possessing several activities. This review is concerned on the synthesis of bioactive pyrazolinone and pyrazolidinedione derivatives (**Fig. 1**).



(1) 3,5-pyrazolidinedione

(2) 1,2-dihydropyrazol-3-one

Fig. 1. Structure of compounds **1-2**

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3,5-Pyrazolidinediones

The increasing importance of 3,5-pyrazolidinediones was due to their use as medical derivatives such as 4-butyl-1,2-diphenyl-3,5-pyrazolidinedione **(3)** which was marked as butazolidin (phenylbutazone). It was widely used in the treatment of rheumatoid arthritis and various other diseases. 3,5-Pyrazolidinediones have also been of interest as color formers in color photography. Five isomeric forms of 3,5-pyrazolidinediones (1) are theoretically possible **(4)**, **(5)**, **(6)**, **(7)** and **(8)** (**Fig. 2**).

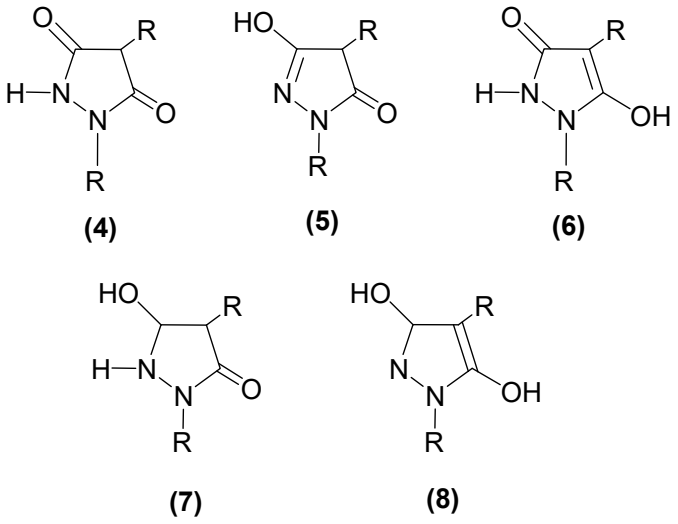


Fig. 2. Structure of compounds **4-8**.

Pyrazolinone

The history of pyrazolinone really began with the synthesis of the first pyrazolinone through the reaction of ethyl acetoacetate with phenylhydrazine by the well-known German chemist, Ludwig Knorr.[6] The resulted compound was 3-methyl-1-phenyl-2-pyrazolin-5-one **(9)**. On the basis of analysis, method of preparation and reactions, pyrazolones are classified as follows: 3-pyrazolin-5-one **(10)**, 2-pyrazolin-5-one **(11)** and 2-pyrazolin-4-one **(12)**. Within each class of pyrazolones many tautomeric forms are possible for simplicity only one form is shown (**Fig. 3**).

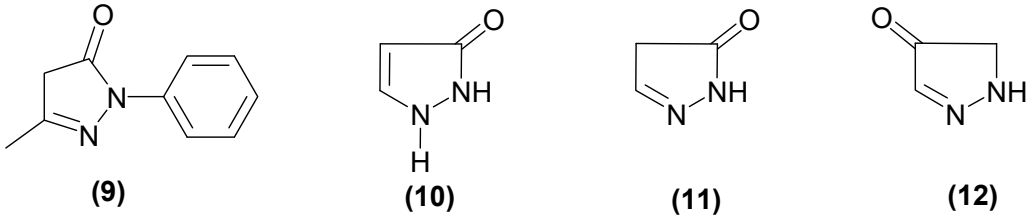


Fig. 3. Structure of compounds **9-12**

2. Synthetic routes

2.1 Synthesis of 3,5-pyrazolidinedione derivatives.

The condensation of some hydrazine derivatives with carbon suboxide was reported to produce the products in 80-90% yield. The use of N,N-diphenyl-N-butylhydrazine in this condensation led to the formation of 4-but-1,2-diphenyl-3,5-pyrazolidinedione **(13)** (**Fig. 4**).[7]

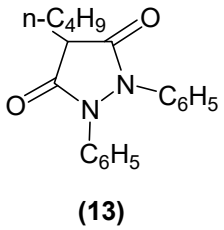
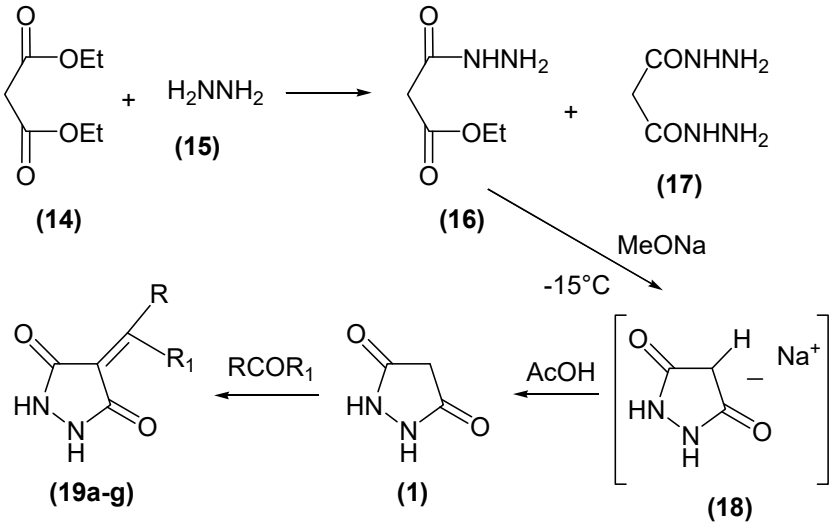


Fig. 4. Structure of compound **13**

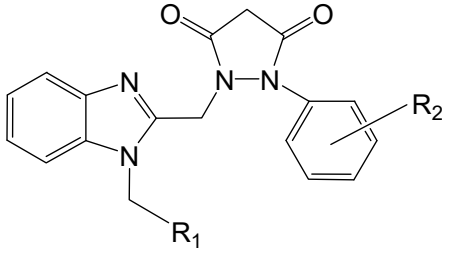
A novel series of 3,5-pyrazolidenedione derivatives were reported. This includes 4-arylidene (alkylidene or aralkylidene)-3,5-pyrazolidinediones **(19a-g)**, which on epoxidation gave unreported oxiranes. The synthesis of these derivatives **(19a-g)** were based on either Knoevenagel reaction of carbonyl derivatives with 3,5-pyrazolidinedione or cyclization of arylidene (alkylidene) malonic acid hydrazide with glacial acetic acid (**Fig. 5**).[8]



19a: R= R_1= Me; **b-f**: R= H, **b**: R_1= p-BrC_6H_4, **c**: R_1= p-ClC_6H_4, **d**: R_1= p-OHC_6H_4, **e**: R_1= p-$Me_2NC_3H_3$, **f**: R_1= p-MeC_6H_4, **g**: R+R_1= 4-(indoxyl-3-yl).

Fig. 5. Structure of compounds **19a-g**

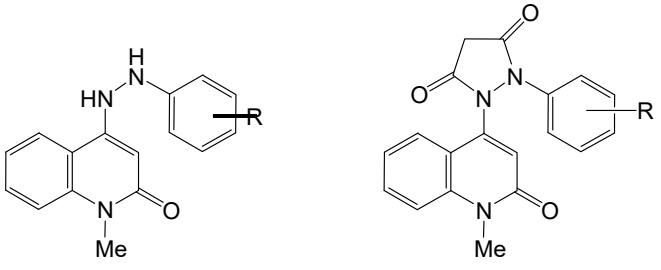
A novel series of Mannich bases 1-((1-substituted ethyl-1H-benzo[d]imidazol-2-yl)methyl)-2-substitued phenyl-pyrazolidine-3,5-dione **(20)** (R_1= $N(Me)_2$, $N(Ph)_2$, piperidino, etc.; R_2= H, 2-Me) were synthesized and evaluated as antinociceptive agents (**Figure 6**).[9]



(20)

Fig. 6. Structure of compound **20**

A series of pyrazolidine-3,5-diones **(22)** (R= 2-Cl, 4-Cl, 2,4-Cl_2, 2-Me, 4-Me, 2-OMe, 2-NH_2, 4-NH_2) were prepared via reaction of hydrazinylquinolones **(21)** with diethyl malonate and evaluated asantinociceptiveagents (**Fig. 7**).[10]



(21) **(22)**

Fig. 7. Structure of compounds **21** and **22**

Several substituted triazenes dyes **(26)** were synthesized by coupling functionalized pyrazolidin-3,5-dione derivatives to various heteroareneazides in excellent yields (98%). The starting Azidopyrazolidindione **(25)** was obtained by the steps illustrated in (**Fig. 8**).[11]

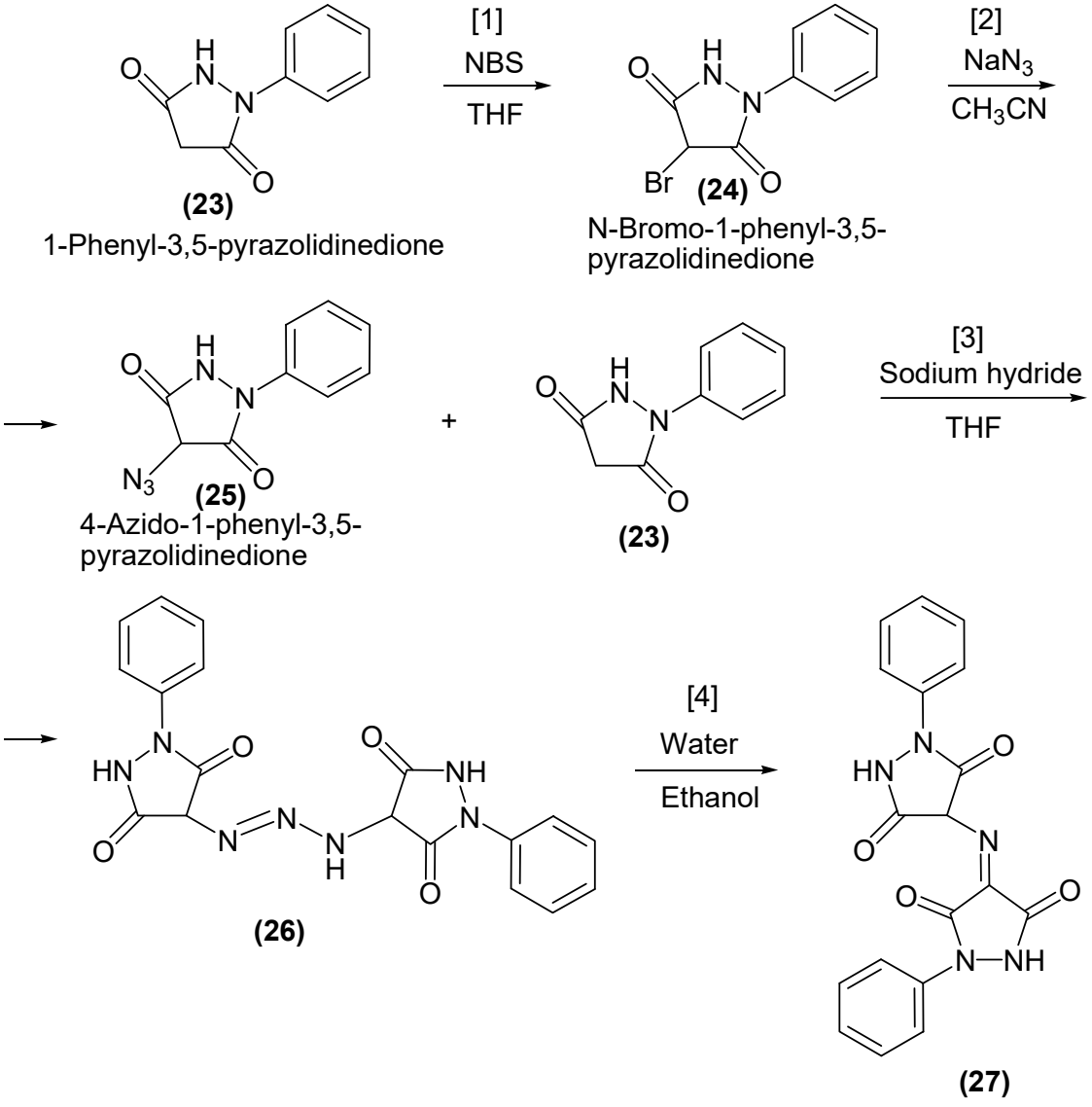


Fig. 8. Structure of compound **27**

Pyrazolidinedione derivatives **(28)** [R_1= H, (cyclo) alkyl, aryl, arylalkyl, heteroaryl, etc.; R2 = (hetero)aryl] are synthesized and have been used for vascular of cardiovascular and of cerebrovascular diseases or conditions associated with platelet aggregation, particularly thrombosis.[12] For instance, 4-(2,3-dimethyl-4-propoxybenzylidene)-1-phenylpyrazolidine-3,5-dione is synthesized from 1-phenylpyrazolidine-3,5-dione and 2,3-dimethyl-4-propoxybenzaldehyde **(Fig. 9)**.

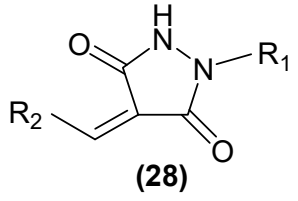


Fig. 9. Structure of compound **28**

Pyrazolidinedione derivatives **(29)** (R= H, MeO, Cl) are prepared by nucleophilic addition of 1-phenyl-3,5-pyrazolidinedione to chalcones. Reactions of **(29)** with $PhNHNH_2$, $H_2NNH_2.H_2O$, $HONH_2.HCl$ and aromatic amines afford the corresponding phenylhydrazoneds, diazepine derivatives, oximes and arylidene derivatives (**Fig. 10**).[13]

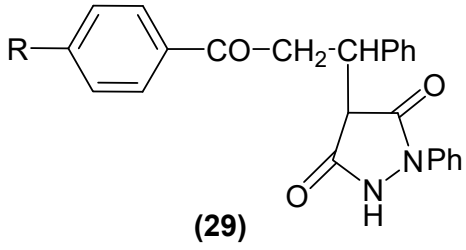


Fig. 10. Structure of compounds **29**

Condensation of 2-pyrrolyl-, 2-thienyl-, or 2-furylcarbaldehyde with 1,2-diphenyl-3,5-pyrazolidinedione gave arylidenepyrazolidine-diones **(30)** (X= NH, S, O) in 35-70% yield. Compound **(30)** (X= NH, S, O) reacted with HCN to give compound **(31)** (X= NH, S, O; R= CN) in 35-60% yield (**Fig. 11**).[14]

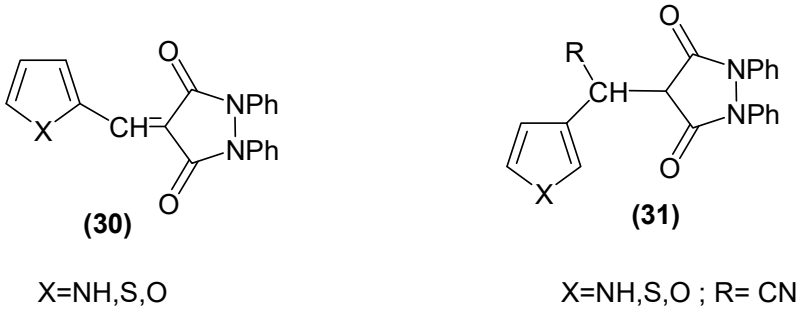


Fig. 11. Structure of compounds **30-31**

4-Substituted derivatives of 1,2-diphenyl-3,5-dioxopyrazolidine **(33)** was described. Refluxing approximately equimolar amounts of Na, 1,2-diphenyl-3,5-pyrazolidine **(32)** and $Me_3CCOCH_2CH_2NMe_2$ in BuOH solution gave 96-7.5% title compound **(33)** (R= Me_3C). Similar treatment of **(32)** with $MeCOCH=CH_2$ yielded 80.4% **(33)** (R= Me) that exhibited potential anti-phlogistic, analgesic and anti-rheumatic activity (**Fig. 12**).[15]

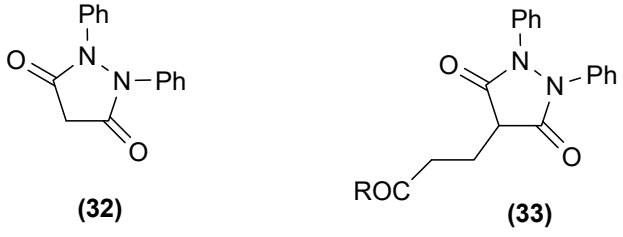


Fig. 12. Structure of compounds **32-33**

4-(3-Methyl-2-butenyl)-1,2-diphenyl-3,5-dioxopyrazolidine feprazone **(36)**, a useful analgesic anti-inflammatory drug was prepared by the condensation of **(34)** (M= alkalimetal salt) with $Me_2C=CHCH_2OAc$ **(35)** in the presence of a Pd complex catalyst. Thus, **(35)**, Tetrakis (Ph_3P, triphenylphosphine) palladium (0) in anhydrous THF were stirred for at room temperature, **(34)** (M= Li) was added under N_2 to give **(36)** (**Fig. 13**).[16]

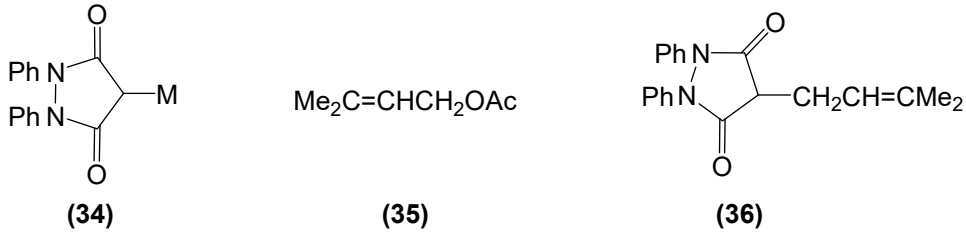


Fig. 13. Structure of compounds **34-36**

4-Prenyl-1,2-diphenyl-3,5-pyrazolidinedione **(37)** was prepared by condensation of $Me_2C{=}CHCH_2CH(CO_2Et)_2$ with $(PhNH)_2$ in EtOH in the presence of EtONa. Compound **(37)** has anti-inflammatory activity in the rate comparable to that of phenylbutazone, but is less ulcerogenic (**Fig. 14**).[17]

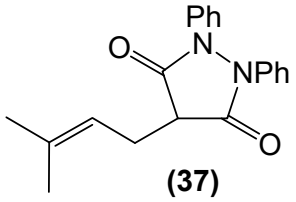


Fig. 14. Structure of compound **37**

The pyrazolidinediones **(38)** (R= $CH_2NR_1R_2$; R_1 and R_2= H, $C_{1\text{-}6}$ alkyl; R_1R_2N= heterocyclyl) were prepared for use as blood platelet aggregations inhibitors. Thus, **(38)** (R= H) was heated with CH_2O and 1-methylpiperazine in Me_2CHOH to give **(38)** (R= 4-methylpiperazinomethyl) (**Fig. 15**).[18]

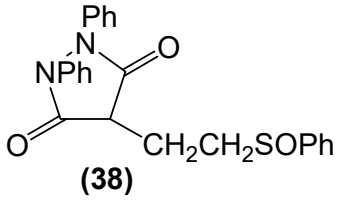


Fig. 15. Structure of compound **38**

Reactions of 1-phenyl-3,5-pyrazolidinedione with N-bromo-succinimide as well as carbonyl compounds were carried out to give **(39)** derivatives 4-Arylidene-1-phenyl-3,5-pyrazolidinediones were reacted with alkylating agents and/or acylating reagents to give the N-alkyl and/or N-acyl derivatives **(40-43)** (**Fig. 16**).[19]

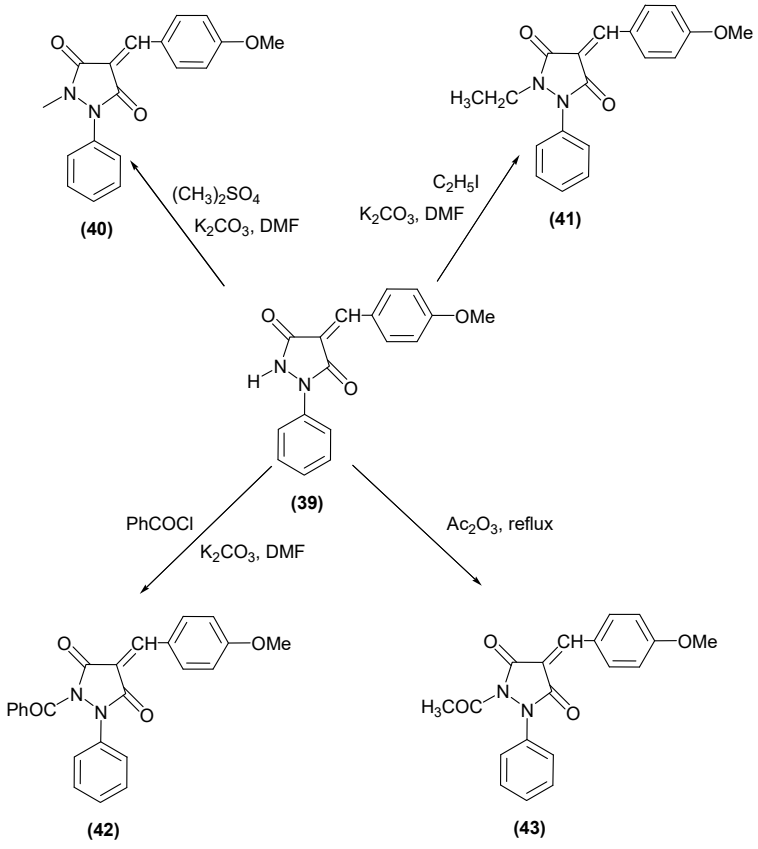


Fig. 16. Structure of compounds **39-43**

2.2 Synthesis of Pyrazolinone derivatives

1-(3-bromophenyl)-4-dicyanomethylene-3-methyl-2-pyrazolin-5-one **(44)** was synthesized by reaction of tetracyanoethylene (TCE) with 3-methyl-1-(3-bromophenyl)-2-pyrazolin-5-one. Compound **(44)** was treated with N,N-dimethylaniline to give very stable violet compound **(45)** . Also compound **(44)** was refluxed with glycine to yield the pyrazolone derivative which reacted with N-phenyl malimide to give the cycloadduct **(46)** (**Fig. 17**).[20]

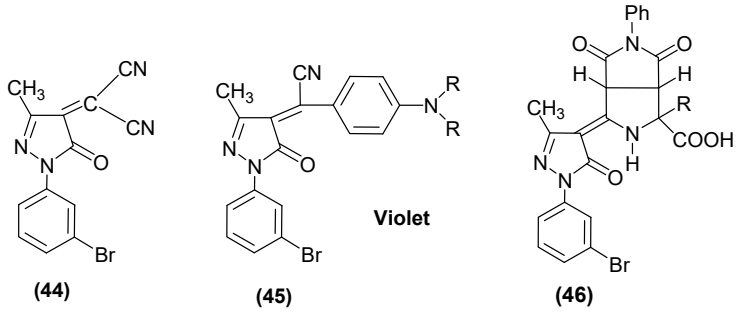


Fig. 17. Structure of compounds **44-46**

Regio- and diastereoselective synthesis of bis-[spiro-pyrazoline-4,5'-pyrazoline] derivatives **(47)** [R_1= C_6H_5, 4-MeC_6H_4, 4-ClC_6H_4; R_2= C_6H_5, 4-MeC_6H_4, 4-ClC_6H_4, 4-$MeOC_6H_4$, 4-$NO_2C_6H_4$, 2-thienyl] by 1,3-dipolar cycloadditon of bis-hydrazonyl chlorides $Ar_1HNN=C(Cl)C(Cl)= NNHAr_1$ with 4-arylidenepyrazoil-5-one derivatives was reported. The cycloaddition route was optimized under both ultrasonic irradiation and conventional heating modes (**Fig. 18**).[21]

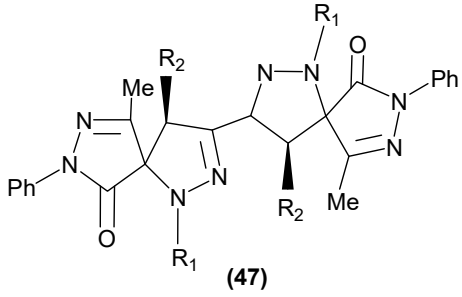


Fig. 18. Structure of compound **47**

The invention provides compounds of formula **(48)** and the pharmaceutically acceptable salts thereof, which are inhibitors of the ROMK (Kir 1.1) channel. The compounds may be used as diuretic and/or natriuretic agents and or the therapy and prophylaxis of medical conditions associated with excessive salt and water retention. Compounds of formula **(48)** wherein Z is (un)substituted-4-(tetrazol-1-yl)phenyl, (un)substituted oxoisobenzofuranyl, (un)substituted (tetrazol-1-yl) pyridinyl, etc.; R_1 is H, F, OH, C_{1-3} alkyl and C_{1-3}alkoxy; R_2 is H and C_{1-4} alkyl; R_3 and R_4 are independently H and (un)substituted C_{1-3} alkyl; R_5 is H, halo, C_{3-6}cycloalkyl and C_{1-3} alkyl; R6 is absent, H and (un)substituted C_{1-3} alkyl; n is 0 and 1; and pharmaceutically acceptable salts thereof, are claimed. Example compound **(49)** was prepared by addition of 2-(3-methyl-5-oxo-2,5-dihydrofuran-3-yl)-2,3,8-triazaspiro-[4,5]decan-1-one to 4-methyl-5-(oxiran-2-yl)isobenzofuran-1-(3H)-one. The invention compounds were evaluated for their ROMK channel inhibitory activity (**Fig. 19**).[22]

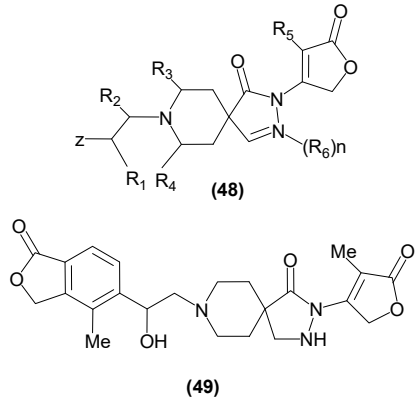


Fig. 19. Structure of compounds **48-49**

The mono- and bis-(p-fluorophenyl)hydrazones of dehydro-L-ascrobic acid were prepared. Oxidation of the bis(hydrazone) **(50)** afforded anhydrohexulosonolactone (p-flourophenyl)hydrazone **(51)**. Rearrangement of **(50)** gave pyrazolindione (p-fluorophenyl)hydrazone, **(52)** whose periodate oxidation gave 3-formyl-1-(p-fluorophenyl)pyrazolin-4,5-dione-4(p-fluorophenyl)hydrazone that upon reduction gave 1-(p-fluorophenyl)-3-hydroxymethylpyrazolin-4,5-dione-4-(p-fluorophenyl) hydrazone **(53)** (**Fig. 20**).[23]

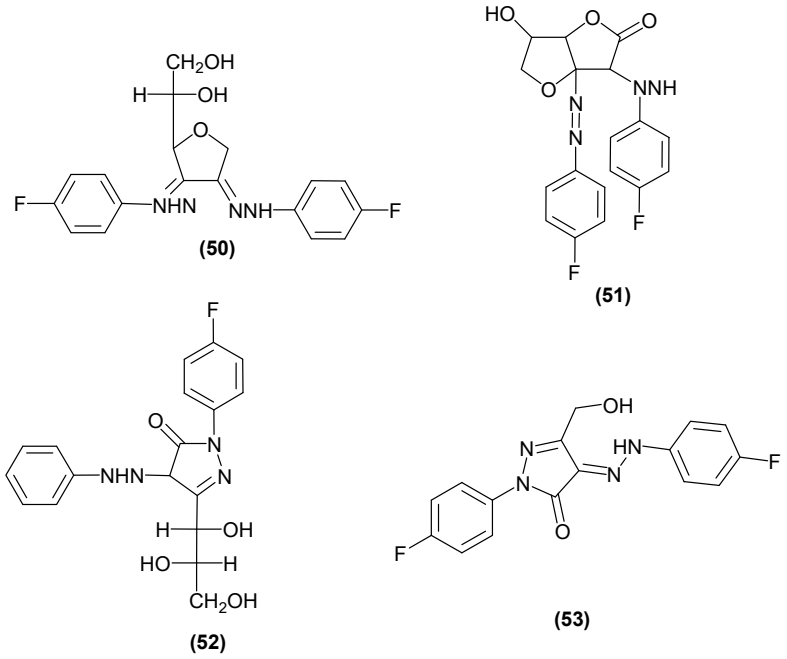


Fig. 20. Structure of compounds **50-53**

β-(3-Hydroxypyrazol-1-yl) ketones, e.g., **(55)** (R_1= Me, R_2= $CH_3(CH_2)_4$, R_3= Me) were prepared in high yields and excellent enantioselectivities (94-98% ee) via a Michael addition reaction between 2-pyrazolin-5-ones **(54)** (R_1= Me, Et, n-Pr) and aliphatic acyclic α,β-unsaturated ketones (E)-R_2CH=$CHCOR_3$ using 9-epi-9-amino-9-deoxyquinine as catalyst (**Fig. 21**).[24]

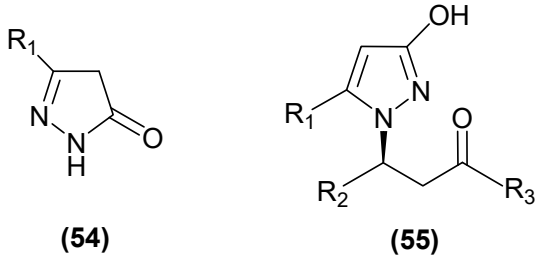


Fig. 21. Structure of compounds **54-55**

Pyrazoline derivative **(57)** (R_1= Me, Et; R_3= H, hydropcarbyl) is synthesized by allowing to react 2-aryl-2-cyanoacetic acid ester **(56)** (R_2= Me, Et) with R_3NHNH_2 in xylene (**Fig. 22**).[25]

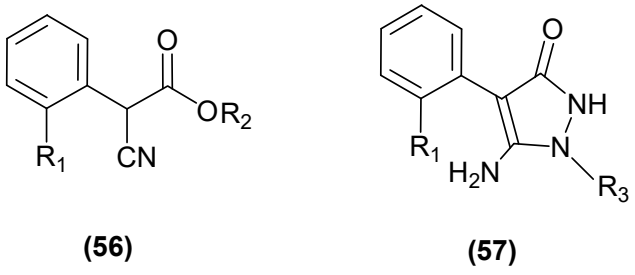
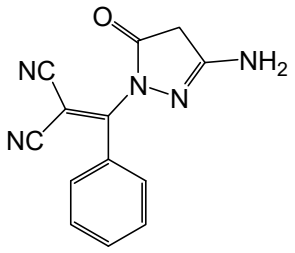


Fig. 22. Structure of compounds **56-57**

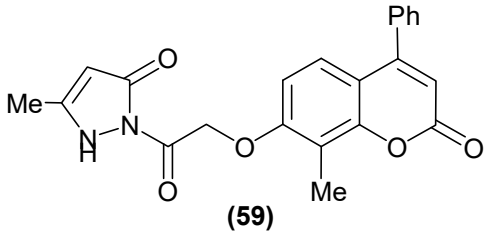
Treatment of 3-Amino-2-pyrazolin-5-one with arylidenemalono-nitriles afforded adducts, 2-(3-amino-5-oxo-4,5-dihydro-*1H*-pyrazol-1-yl(phenyl)methylene)malononitrile **(58)** (**Fig. 23**).[26]



(58)

Fig. 23. Structure of compound **58**

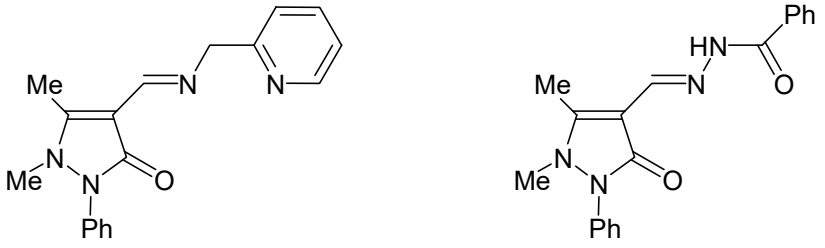
Novel series of 7-substituted-benzopyran-2-ones was synthesized by incorporating heterocyclic rings as oxadiazole, triazole, pyrazole or pyrazolin-5-one to benzopyran-2-one nucleus at pH 7 via methylene-oxy or acetoxy linker. Among them, compound **(59)** that exhibited broad spectrum antitumor activity (**Fig. 24**).[27]



(59)

Fig. 24. Structure of compound **59**

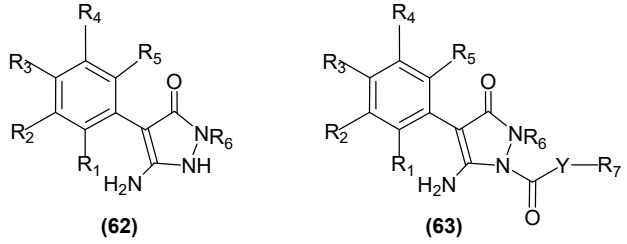
Two series of complexes of two Schiff bases, 2,3-dimethyl-1-phenyl-4-(pyridine-2-ylmethyliminomethyl)-3-pyrazolin-5-one (**60**) and 4-formyl-2,3-dimethyl-1-phenyl-3-pyrazolin-5-one benzoylhydrazone (**61**) with the general compounds [Ln(**60**)$_2$(ClO_4)$_2$](ClO_4) and [Ln(**61**)$_2$(ClO_4)](ClO_4)$_2$ (Ln= Y, La, Pr, Nd, Sm, Eu, Gd, Dy, Ho or Er) were synthesized and characterized. Both **(60)** and **(61)** are neutral ligands coordinating through the carbonyl oxygen(s) and the azomethine nitrogen in these complexes (**Fig. 25**).[28]



(60) **(61)**

Fig. 25. Structure of compounds **60-61**

Compounds **(62)** [R_1-R_5= H, halo, (halo)-substituted Me; R_6= H, C_{1-5} alkyl] are reacted with $XCOYR_7$ (X= Cl, Br; Y= O, S; R_7= C_{1-5} alkyl, C_{3-5} alkenyl, alkynyl) in water/organic solvent mixtures in the presence of bases to afford reaction mixtures, which are separated from oil phase, and mixed with acids and heat treated to afford aq. slurries. The slurries are then heat treated and then solid-liquid separated to afford **(63)** of minimized urea content that used as agrochemical materials (**Fig. 26**).[29]



(62) **(63)**

Fig. 26. Structure of compounds **62-63**

A process for producing a pyrazolinone derivative **(65)**; R_1-R_5=H, halo, halomethyl, Me; R_6= H, C_{1-6} alkyl; R_7= C_{1-5} alkyl, C3-5 alkynyl; Y= O, S) is introduced, which is characterized by: reacting of pyrazolinone compound **(64)** ; R_1-R_6= same as above) with an acid halide of formula XCO-Y-R_7 (X= Cl, Br; Y, R_7= same as above) in a mixed solution of water and an organic solvent in the presence of a base; subjecting the resulting reaction mixture to the oily-layer/aq.-layer separation; adding an acid to the aqueous layer to neutralize the aqueous layer, thereby causing the precipitate of the pyrazolinone derivative **(65)**; and separating the pyrazolinone derivative **(64)**. This process gives pyrazolinone derivative **(65)** in good yield with high quality (**Fig. 27**).[30]

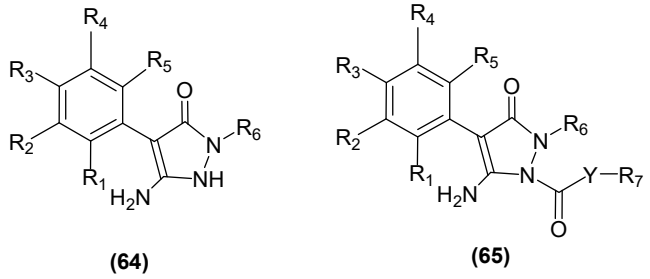


Fig. 27. Structure of compounds **64-65**

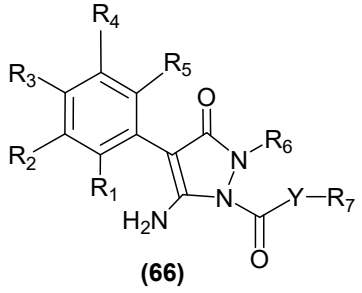


Fig. 28. Structure of compound **66**

Compound **(66)** (R_1-R_5 = H, halo, (halo-substituted) methyl; R_6 = H, alkyl; Y = O, S; R_7 = alkyl, alkenyl, alkynyl] was produced by reacting 3-amino-4-phenylpyrazolin-5-one derivative with compound $XCOYR_7$ [X= Cl, Br; Y= O, S; R_7= alkyl, alkenyl, alkynyl] in water and an organic solvent in the presence of a base (**Fig. 28**).[31]

Ternary condensation of 3-methyl-1-phenyl-2-pyrazolin-4,5-dione **(67)**; malononitrile and primary amines gave arylaminocyanomethylene derivatives **(68a-d)**, while using tertiary amines, the unexpected products, bis-p-(N,N-dialkylaminophenyl)malononitriles **(70a-b)** (**Fig. 29**).[32]

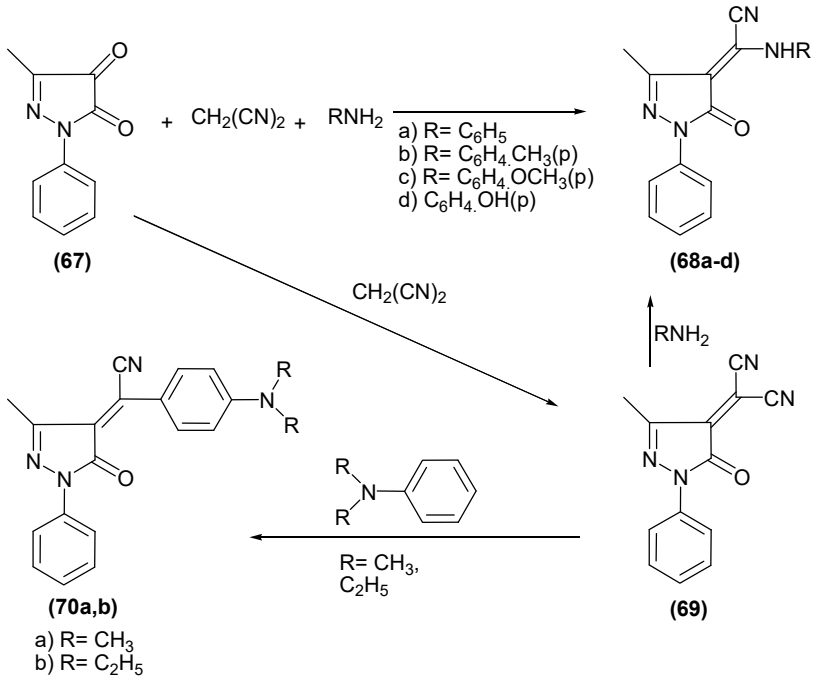


Fig. 29. Structure of compounds **67-70**

4-(Dicyanomethylene)-3-methyl-1-phenyl-2-pyrazolin-5-one **(69)** undergoes cycloaddition reaction in a normal or inverse electron demand Diels-Alder reaction to give the cycloadducts **(71-72)** (**Fig. 30**).[33]

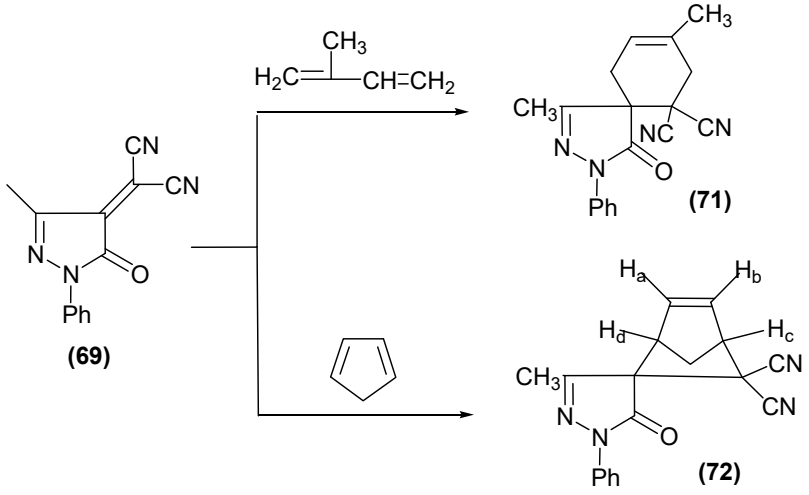


Fig. 30. Structure of compounds **71-72**

1-(2-Benzothiazolyl)-4-(dicyanomethylene)-3-methyl-2-pyrazolin-5-one **(75)** was prepared by treating 2-(2-benzothiazolyl)-1,2-dihydro-5-methyl-3H-pyrazol-3-one **(73)** with tetracyanoethylene **(74)**. Compound **(76)** was used in preparation of some heterocyclic compounds **(77-80)** by treating with malononitrile, ethyl cyanoacetate, 3-methyl-2-pyrazolin-5-one derivatives and acetyl acetone respectively (**Figs. 31, 32**).[34]

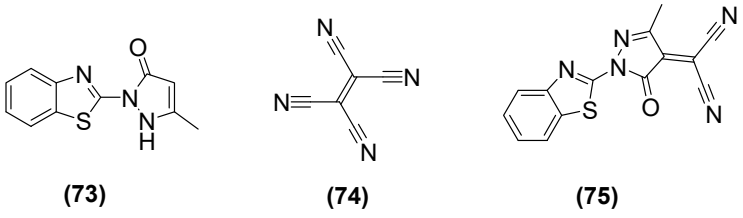


Fig. 31. Structure of compounds **73-75**.

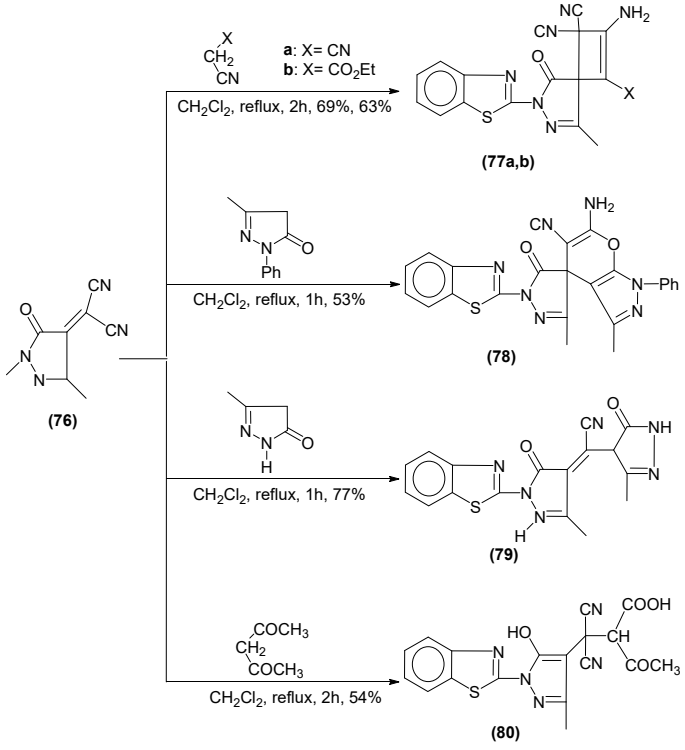


Fig. 32. Structure of compounds **76-80**

1,3-Dihydro-3-(3',5'-dioxo-2'H-1'-phenylpyrazolidine)-2H-indol-2-one **(82)** was synthesized via reaction of compound **(23)** with compound **(81)**, and its reactions with active methylene derivatives, amines, semicarbazide hydrochloride and thiosemicarbazidewere studied (**Fig. 33**).[35]

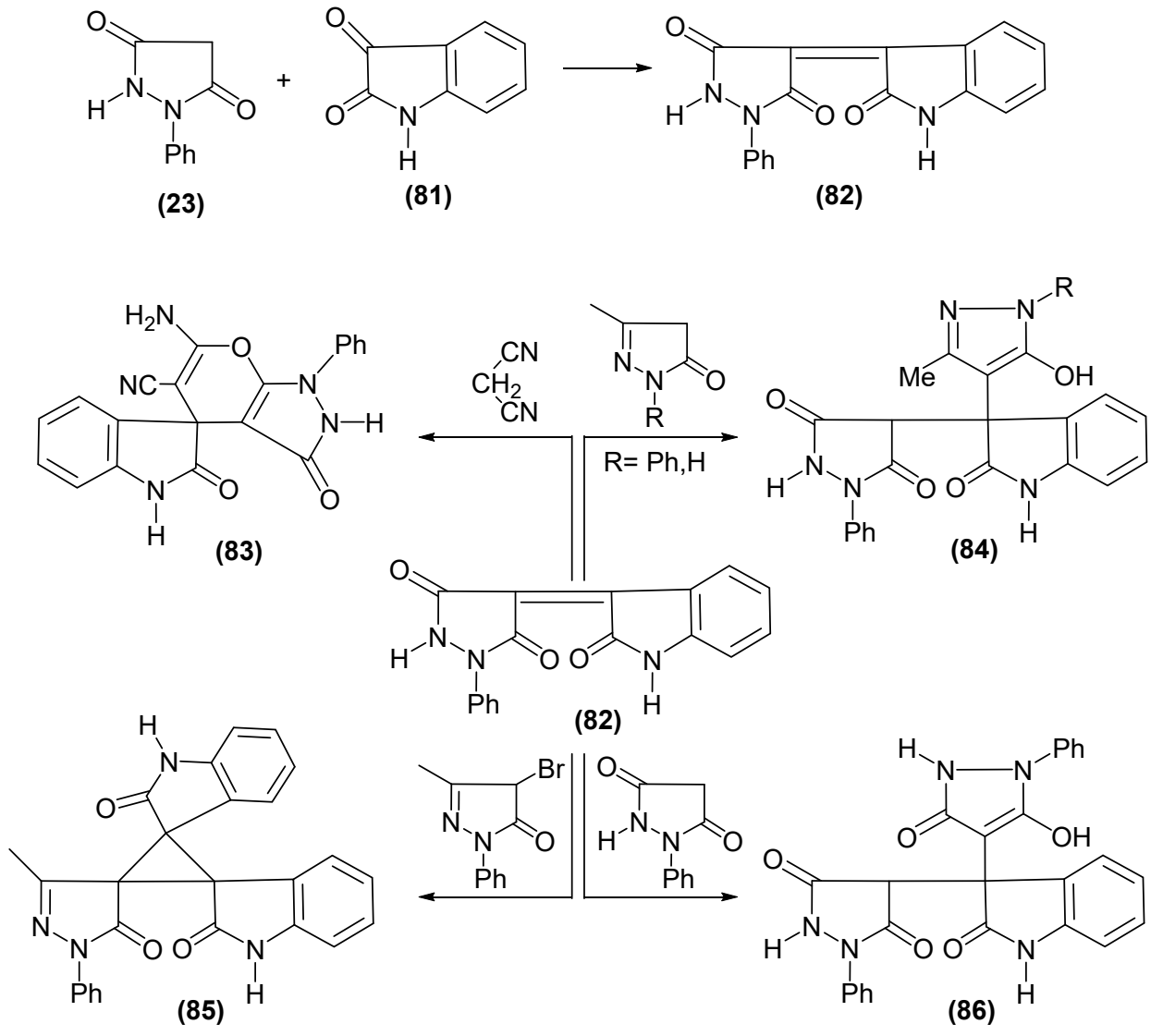


Fig. 33. Structure of compounds **81-86**

3-Methyl-1-phenyl-2-pyrazoline-4,5-dione **(67)** condenses readily with malononitrile in refluxing ethanol to yield 4-(dicyanomethylene)-3-methyl-1-phenyl-2-pyrazolin-5-one **(69)**. Compound **(69)** reactswith aliphatic, aromatic and heterocyclic amines to yield 4-substituted (aminocyano-methylene)-3-methyl-1-phenyl-2-pyrazolin-5-ones **(89)** (**Fig. 34**).[36]

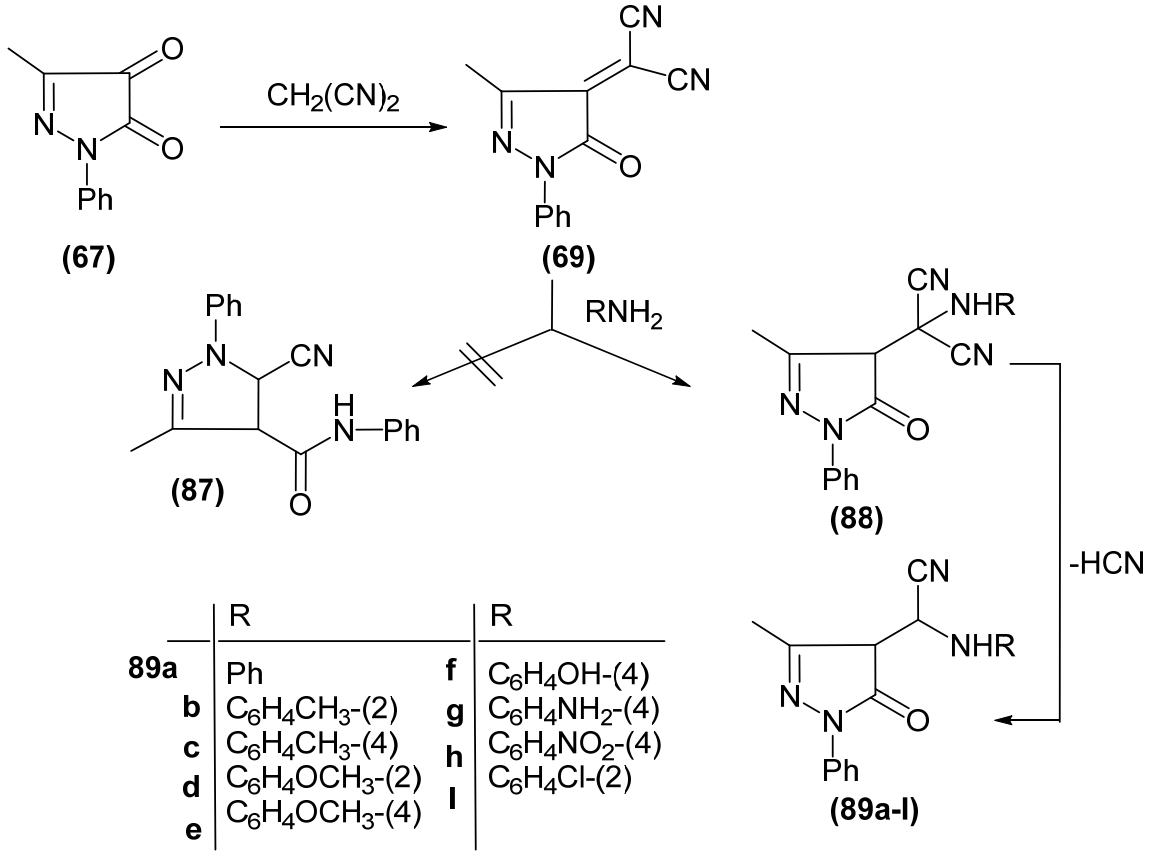
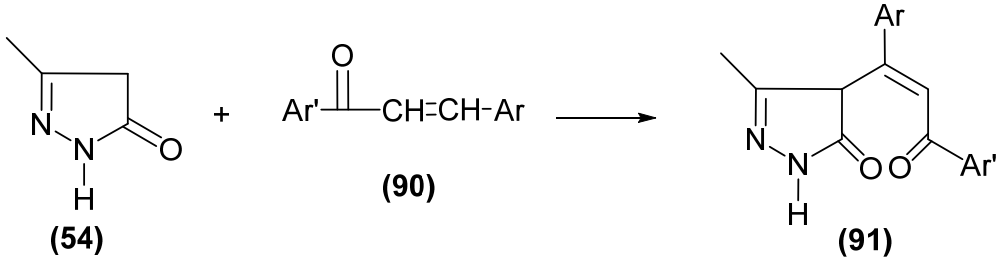


Fig. 34. Structure of compounds **67**, **69**, and **87-89**

3-Methyl-4(1-Ar-3-Ar-3-oxo-pyropyl)-2-pyrazolin-5-ones **(91)** were synthesized by the interaction of 3-methyl-2-pyrazolin-5-one **(54)** with chalcones **(90)** in n-butanol (**Fig. 35**).[37]



Ar	Ar'
C_6H_5	C_6H_5
C_6H_5	p-$CH_3C_6H_4$
p-ClC_6H_4	1-naphthyl
p-$CH_3C_6H_4$	1-naphthyl
p-$CH_3OC_6H_4$	1-naphthyl

Fig. 35. Structure of compounds **54**, **90-91**

4-Nitroso-3-methyl-2-pyrazolin-5-one **(92a,b)** reacts readily with diazoalkanes or the corresponding alkyl halides to yield exclusively the 4-alkyl derivatives of oxazoles or the corresponding nitrones are formed. The isonitroso derivatives **(92a,b)** undergo condensation with primary aliphatic amines or amino acids to give rubazonic acid derivatives **(95a,b)** (**Fig. 36**).[38] This work is considered important in organic chemistry cause it ensures the significance of organic compounds in different fields.[39-64]

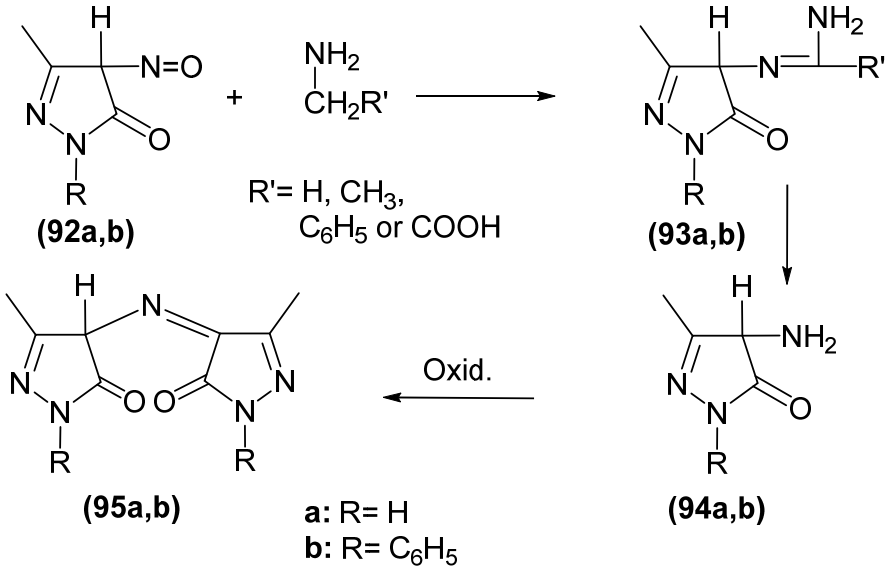


Fig. 36. Structure of compounds **92-95**

3. Conclusion

Pyrazolone, a five-membered nitrogen bearing heterocyclic system can be denoted as pharmaceutically important compounds. Due to the excellent performance in pharmaceutical and agromedical fields of oxo derivatives of pyrazoline and pyrazolidine and the rapidly increasing needs for drugs, the design and synthesis of these of derivatives with structural variety have increasing attentions.

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