Available online www.jocpr.com

Journal of Chemical and Pharmaceutical Research, 2016, 8(5):969-981

ISSN : 0975-7384
CODEN(USA) : JCPRC5

Strategies for chemical synthesis of pyrazolone derivatives and their bio-significance

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ABSTRACT

Over the last few decades, pyrazolone derivatives have been used for various biochemical applications. Some of these derivatives such as metamizole, phenazone, aminopyrine and propyphenazone, are widely used as anti-inflammatory and analgesics. Moreover, pyrazolones have been exhibited antioxidant, antibacterial, anticancer and several other biological activities. Thus, keeping in view of their importance, synthetic strategies for existing as well as novel pyrazolone derivatives have been developed and explored their biochemical utility. As versatile features of pyrozaolones have emerged, so the aim of the present paper is to put chemical synthetic schemes and biological advancements of pyrazolone derivatives together.

Keywords: Pyrazolones, *N*-Arylpyrazolones, Fused-pyrazolones, Spiropyrazolones, bio-activity.

INTRODUCTION

Pyrazolones are five membered nitrogen containing heterocyclic compounds. The 3-pyrazolone (**1**) and 5-pyrazolone (**2**) are most dominant classes having importance in pharmaceutical industry due to their bio-activity (**Figure-1**). The pyrazolones, such as ampyrone, phenazone and propylphenazone are well known for their antipyretic and analgesic activities. Edaravone has been used for treating brain ischemia [1] and myocardial ischemia [2]. Some novel pyrazolones have been possessed antimicrobial [3], analgesic, anti-inflammatory, antipyretic [4], antimycobacterial [5], anticancer [6], gastric secretion stimulatory [7], anticonvulsant [8] and antimalarial activities [9]. Pyrazolones are used as starting materials for the synthesis of commercial aryl/heteroaropyrazolone dyes [10, 11]. Halogenated pyrazolones displayed bio-activities as potent catalytic inhibitor of human telomerase [12] and as fungicide against *Aspergillus niger* and *Helminthosporium oryzae* [13]. Pyrazolones have also been shown anti-HIV [14], anti-diabetic [15], anti-hyperlipidemic [16] and immunosuppressive activity [17]. Thus, advancement in the synthesis or derivatization of pyrazolones and exploration of their applications have been emerged and grown exponentially. Here we describe the various reported strategies for chemical synthesis of pyrazolone derivatives. A light was also put on their various bio-activities. This work will help to recognize the site of modification on pyrazolone skeleton, to design the synthetic strategy and to explore their possible bio-application.

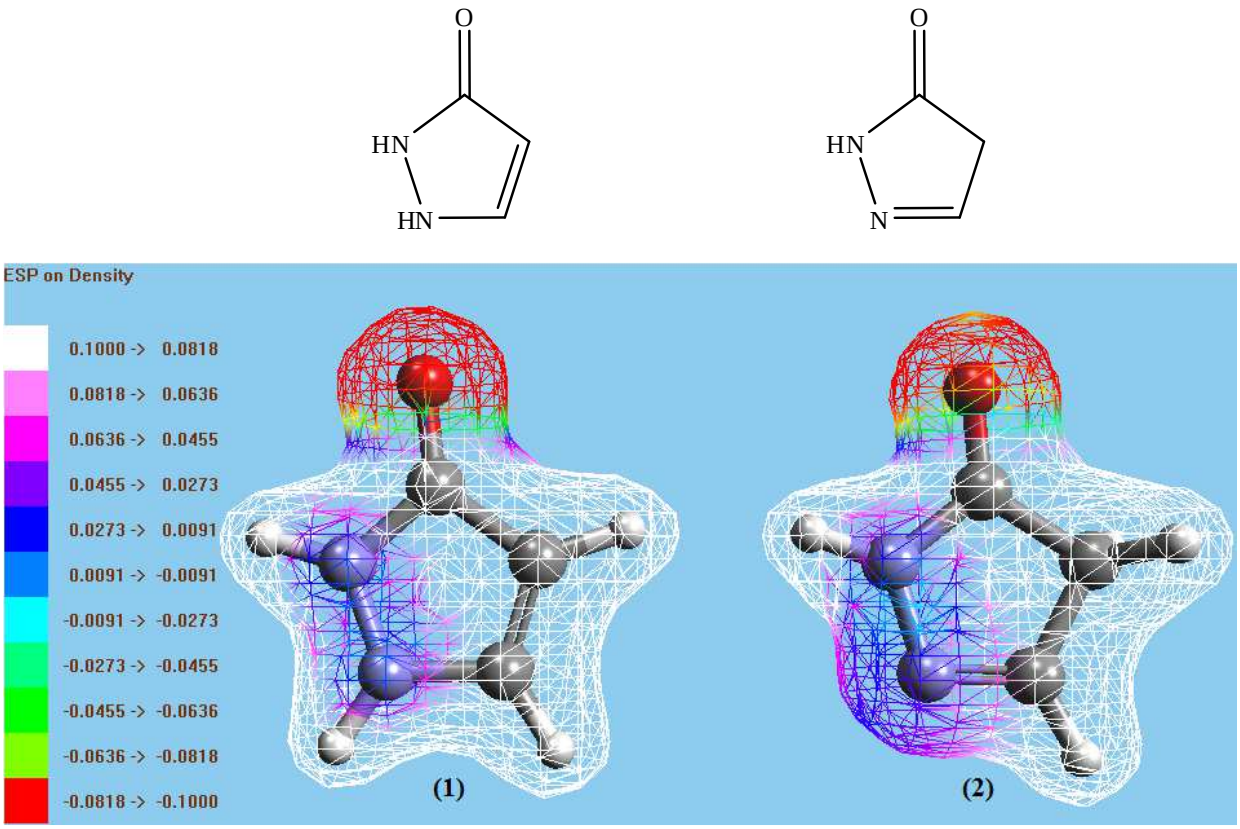
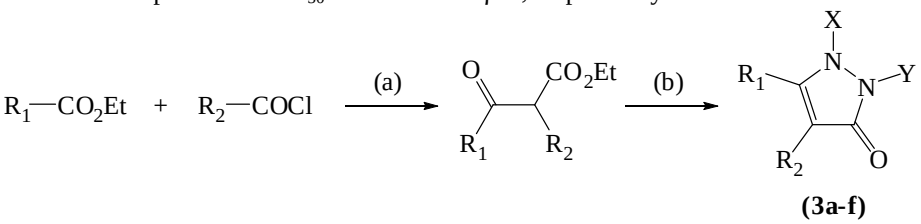


Figure-1. Chemical structures and electrostatic surfaces of 3- and 5-pyrazolone

In a study, Brana *et al*. synthesized bis arylpyrazolones (**3a-f**) using ethyl ester, acyl chloride and hydrazines (**Scheme-1**) [18]. The growth inhibitory activity evaluation in human cell lines (HT-29, HeLa and PC-3) indicated compound **3b** and **3e** as most potent with IC_{50} 11.3 and 46.7 µm, respectively.



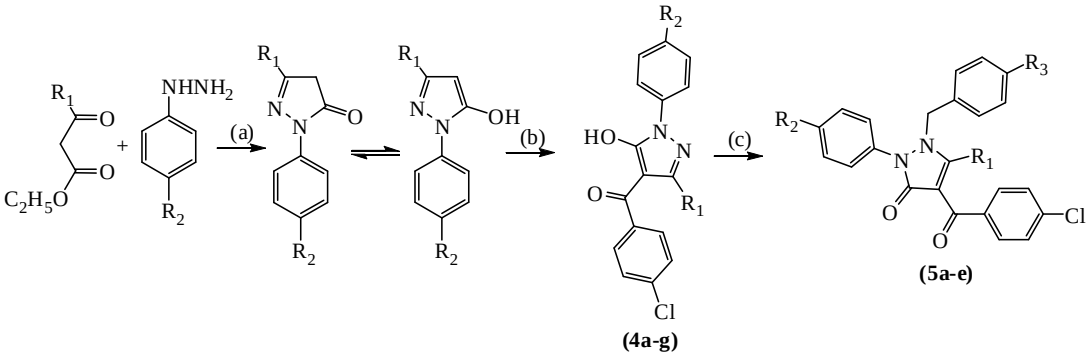
(3a-f)

Scheme-1. Synthesis of bis arylpyrazolones (3a-f): (a) BuLi/THF, DIPA, -78 °C; (b) Camphoric acid/EtOH, X-NH-NH-Y, reflux.

Table-1. Different substitutions on *N,N*-dialkylamino alkyl-substituted bisindolyl and diphenyl pyrazolone derivatives

Entry	R_1	R_2	X	Y
3a	Ph	Ph	H	H
3b	*N*-Methylindolyl	*N*-Methylindolyl	H	H
3c	Ph	Ph	H	$(CH_2)_2N(Me)_2$
3d	Ph	Ph	H	$(CH_2)_2N(Et)_2$
3e	*N*-Methylindolyl	*N*-Methylindolyl	H	$(CH_2)_2N(Et)_2$
3f	Ph	Ph	$(CH_2)_2N(Et)_2$	H

Castagnolo, *et al*. have been synthesized phenyl pyrazolones and converted them into series of corresponding pyrazole derivatives (**4a-g** and **5a-e**) using Buchi Syncore synthesizer (**Scheme-2**) [19]. Their biological evaluation and SAR indicated that small lipophilic substituents in pyrazole ring (R_1) and phenyl ring (R_2) and potentiate the activity as inhibitors of *M. tuberculosis*. The presence of *p*-chlorobenzoyl functionality was found to be essential for antitubercular activity of the compounds.

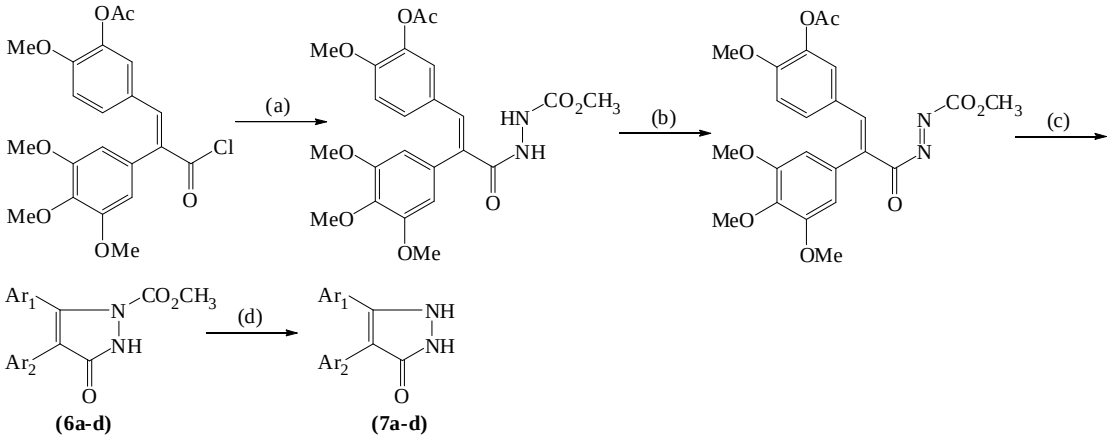


Scheme-2. Synthesis and conversion of pyrazolones to pyrazoles: (a) Polymer bound *p*-toluenesulfonic acid, EtOH, Buchi Syncore, 300 rpm (b) *p*-Cl-benzoyl chloride, $Ca(OH)_2$, dioxane, Syncore, 300 rpm, reflux (c) Benzyl halide, NaH, DMF, NaI, Syncore, 300 rpm

Table-2. Anti-TB profile of benzoyl pyrazoles (4a-g) and benzoyl pyrazolones (5a-5e)

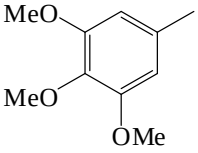
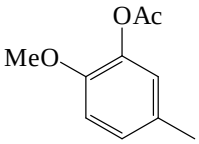
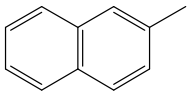
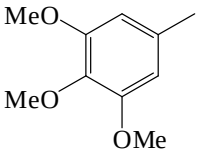
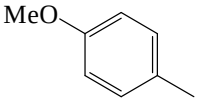
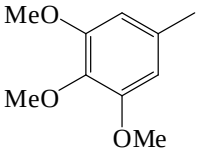
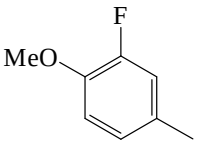
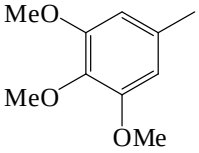
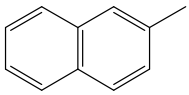
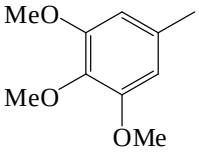
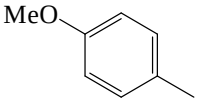
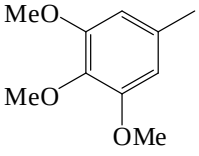
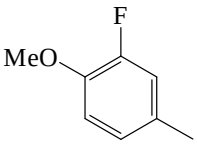
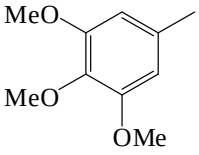
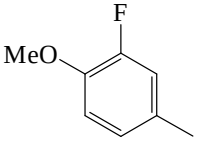
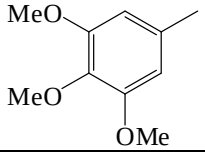
Entry	R_1	R_2	MIC (μg mL^{-1}) *M. tuberculosis*
4a	CH_3	Cl	6.25
4b	CH_3	H	6.25
4c	CH_3	F	12.5
4d	Ph	Cl	16
4e	CH_3	Br	4
4f	CH_3	CH3	16
4g	CH_3	Isopropyl	16
5a	Bn	Cl	16
5b	(*p*-F)Bn	H	32
5c	(*p*-NO_2)Bn	H	>32
5d	Bn	H	>64
5e	(*p*-NO_2)Bn	Cl	32

Burja *et al*. reported synthesis of combretastatin-fused-pyrazolones using multistep strategy (**Scheme-3**) and evaluated for their cytotoxicity and antitubulin activity [20, 21]. Compound **6a-7d** found to be most potent among all tested compounds (**Table-3**). However, only compound **7a-7d** showed tubulin polymerization inhibitory activity ≥ 98%.

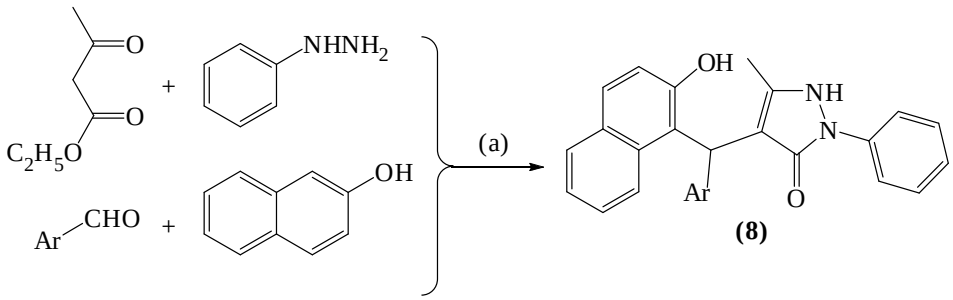


Scheme-3. Synthesis of combretastatin-fused-pyrazolones: (a). $NH_2NHCOCH_3$, Py, DCM, 0°C-rt, 17h; (b). NBS, Py, rt, 10 min; (c). DCM, reflux, 4h; (d). NaOH/MeOH, DCM/MeOH, rt, 31h and HCl

Table-3. Cytotoxicity profile of combretastatin-fused-pyrazolones (6a-7d)

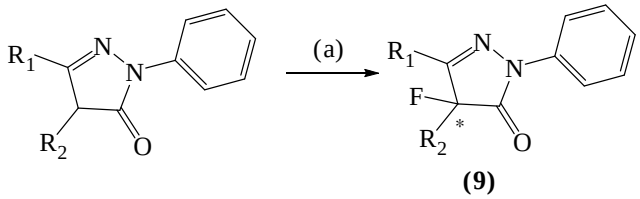
Compound	Ar1	Ar2	IC_{50} (µm)
6a			0.337
6b			0.523
6c			0.959
6d			1.72
7a			0.114
7b			0.152
7c			0.158
7d			0.176

In a study Akondi *et al.* reported Ce/SiO2 catalyzed synthesis of *N*-arylpyrazolone skeleton (**8**) using multicomponent one-pot synthetic strategy under aqueous media with yield of 83-92% (**Scheme-4**). These pyrazolones have been exhibited promising antimicrobial activity against both bacteria and fungi [22].



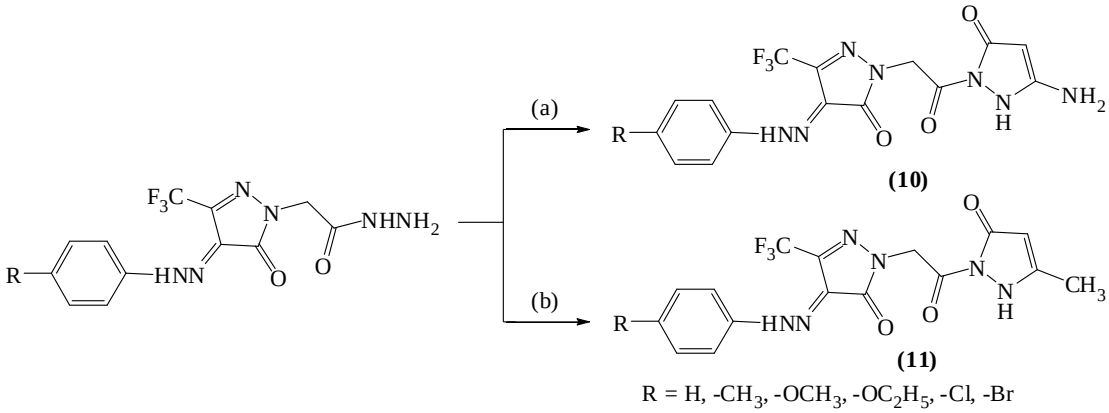
Scheme-4. Multicomponent synthesis of *N*-arylpyrazolones (8): (a) Ce/SiO_2, H_2O, Δ

Very recently, Bao *et al.* synthesized the *N*-arylfluoropyrazolones (**9**) using quinine catalyzed asymmetric fluorination with yield up to 98% (35-81% ee), **Scheme-5** [23].



Scheme-5. Synthesis of *N*-arylfluoropyrazolones (9): (a) *N*-FBS, Quinine, Cs_2CO_3, H_2O, $CHCl_3$, -60 °C

Earlier, Rao *et al.* reported synthesis of bis pyrazolones (**10** and **11**) from hydrazide derivatives of pyarzolone using acid catalyzed condensation-cyclization reaction under reflux conditions (**Scheme-6**) [24]. These bis pyrazolones have been shown comparable antibacterial (against *S. aureus, B. cereus, E. coli and P. aeruginosa*) and antifungal (against *A. niger, C. albicans*) activities.



Scheme-6. Synthesis of 3-amino and 3-methyl bis pyrazolones (10, 11): (a) $CH_3COCH_2COOC_2H_5$, AcOH, EtOH; (b) $CNCH_2COOC_2H_5$, AcOH, EtOH

Sphingosine 1-phosphate receptor 1 (S_1P_1) are known to involve in the pathogenesis of inflammation associated diseases of immune, vascular and nervous systems [25]. The S_1P_1 antagonists are expected to be potential therapeutic agents for cardiovascular disorders and angiogenesis.

In a molecular library screening study, Nakamura *et al*. reported that pyrazolone derivative **12** inhibits S_1P_1 receptors with IC_{50} 17.0 μM [26]. Compound **12** led to the identification novel biphenyl sulfonates as S_1P_1 receptor antagonists.

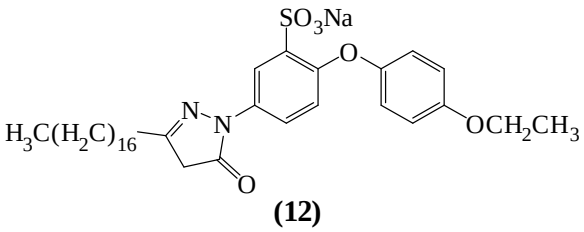
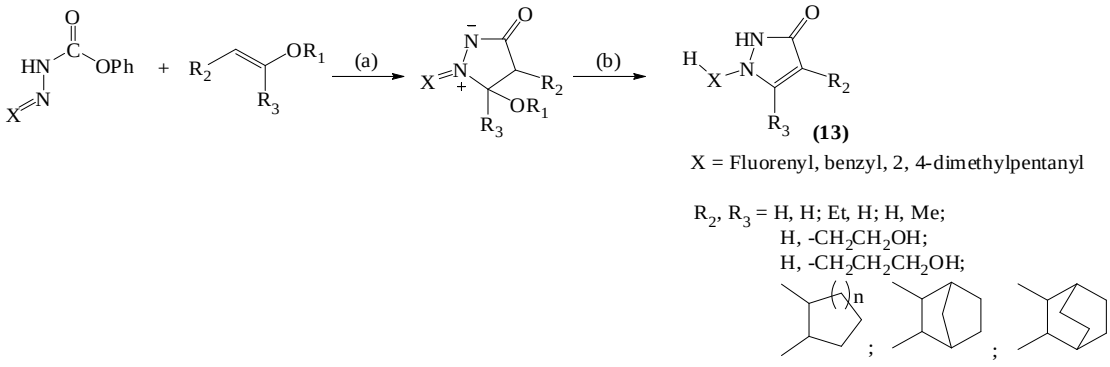


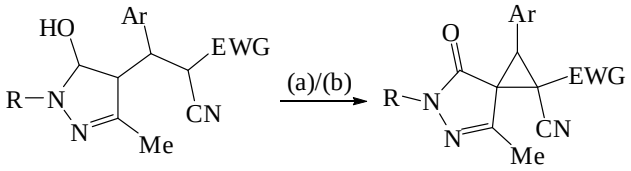
Figure-2. Structure of S_1P_1 receptor antagonizing pyrazolone (12)

Lavergne *et al.* synthesized the *N*-alkylated pyrazolones (**13**) from enol ethers and hydrazones by aminocarbonylation with yield of 45-95% (**Scheme-7**) [27].



Scheme-7. Synthesis of *N*-alkylated pyrazolones: (a) Et_3N, $PhCF_3$ (0.1 M), 70-100 °C (sealed vial); (b) $NaBH_4$, MeOH, -20 °C to rt, then NH_4Cl or NH_4Cl, *p*-TsOH, $CHCl_3$, 60 °C, 3h

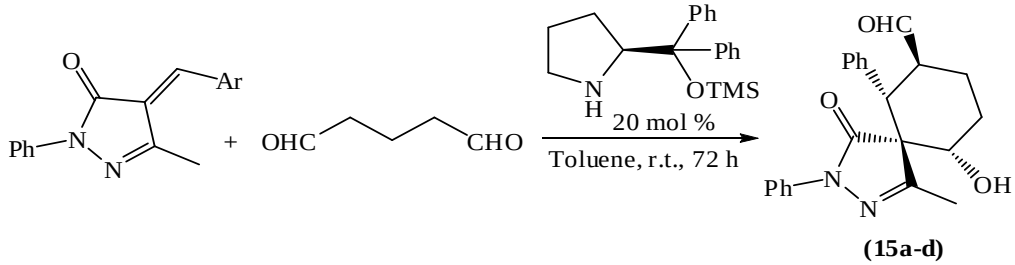
Very recently, Vereshchagin *et al.* reported one pot synthesis of highly strained chiral spiropyrazolones (**14**) using Br_2 assisted cyclization with yield of 61-97% (**Scheme-8**) [28]. Spiropyrazolones are known for their antimicrobial [29], antitumor [30], and anti-trypanosomiatic [31].



(14) a: R= H, Ar= Ph, EWG = CN
b: R= H, Ar= *p*-MePh, EWG = CN
c: R= H, Ar= *m*-BrPh, EWG = CN
d: R= H, Ar= *p*-FPh, EWG = CN
e: R= Ph, Ar= *m*-BrPh, EWG = CN
f: R= H, Ar= *p*-ClPh, EWG = CO_2Me

Scheme-8. Synthesis of spiropyrazolones: (a) Br_2, EtONa, EtOH, r.t., 3h; (b) 0.2M Br_2 in water, EtOH, 40 °C, 1h.

Ceban *et al.* reported a asymmetric synthesis of spiropyrazolones (15a-d) from benzylidenepyrazolones and glutaraldehyde using (*S*)-2-(diphenyl ((trimethylsilyl) oxy) methyl)pyrroline as a catalyst (Scheme-9) [32]. Final products obtained with excellent yields and diastereoselectivities but poor enantioselectivities (Table-4)



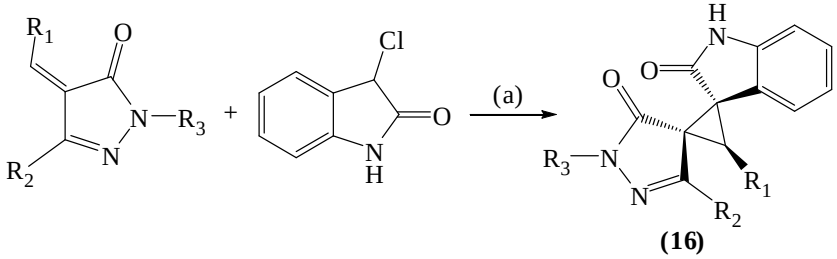
(15a-d)

Scheme-9. Synthesis of spiropyrazolones (15a-d)

Table-4. Diastereoselectivity and yield of spiropyrazolones (15a-d)

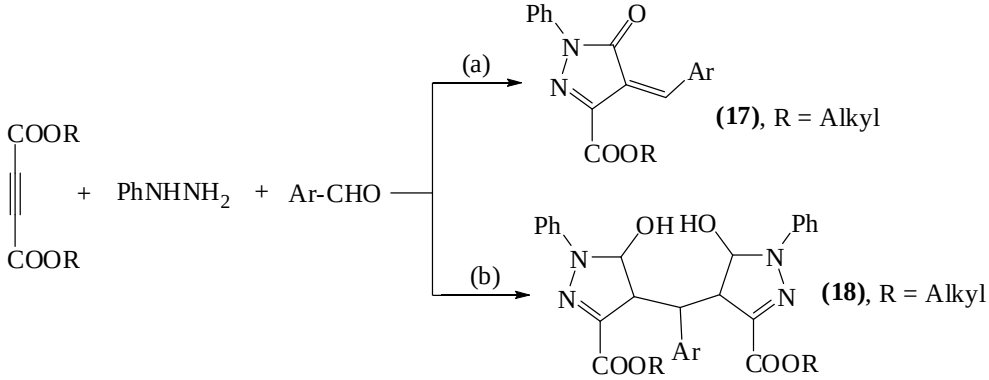
Compound	Ar	Diastereoselectivity (d.r.)	% Yield
15a	Ph	>8:1	72
15b	(*p*-Br)Ph	>8:1	87
15c	(*p*-Me)Ph	11:1	93
15d	(*o*-Cl)Ph	14:1	92

Li *et al.* reported oxindole containing spiropyrazolones (**16**) through DIPEA or squaramide catalyzed diastereoselective Michael/alkylation cascade reactions of arylidenepyrazolones with 3-chlorooxindoles (**Scheme-10**) [33].



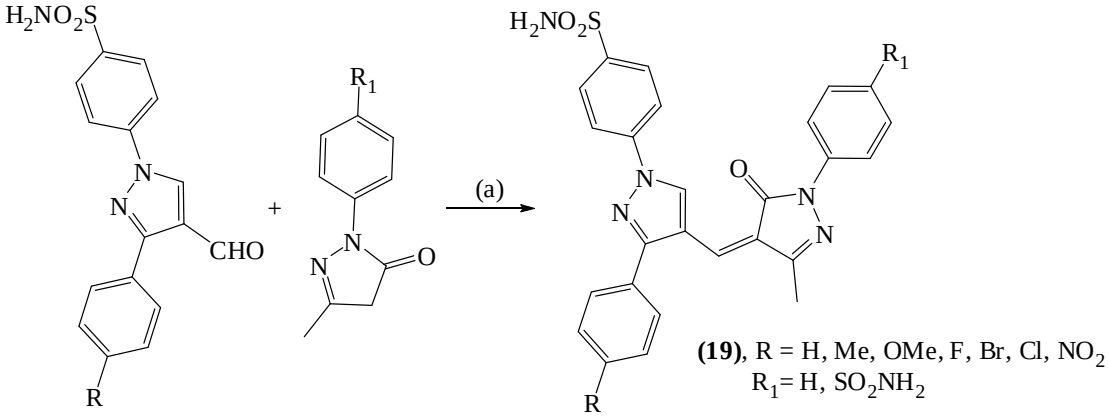
Scheme-10. Synthesis of oxindole containing spiropyrazolones: (a) DIPEA (100 mol%), CH_2Cl_2, r.t. 12-36h or squaramide (5 mol%), K_2CO_3 (100 mol%), CH_3CN

Tu *et al.* synthesized arylidene pyrazolones (**17**) and C-tethered bispyrazol-5-ols (**18**) from acetylenedicarboxylates, phenylhydrazine and aryl aldehydes using multicomponent domino reactions with yield 75-92% (**Scheme-11**) [34].



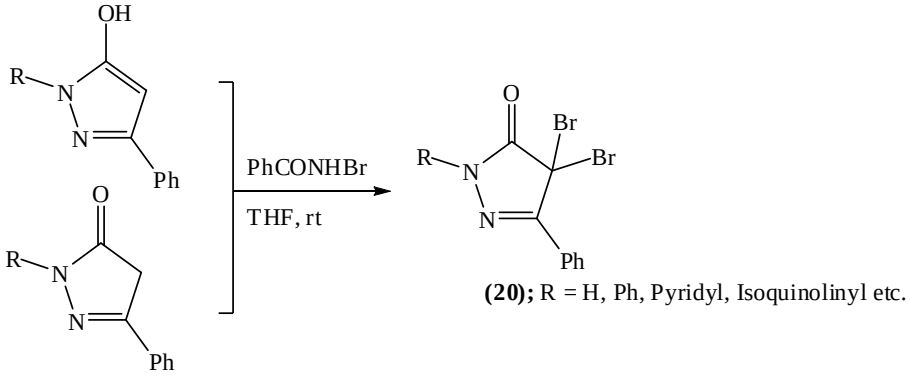
Scheme-11. Synthesis of bispyrazolone and bispyrazol-5-ol: (a) and (b) AcOH, MW or rt, 10 min

Khloya *et al.* reported the synthesis of *N*-aryl 4-aryledine pyrazolones (**19**) from phenyl hydrazine, 4-pyrazolaldehyde and *N*-arylpyrazolone via Knovenagel condensation (**Scheme-12**) [35]. The compounds were found to be active against Gram-positive (*B. subtilis* and *S. aureus*), Gram-negative (*P. fluorescens* and *E. coli*) bacteria as well as pathogenic fungi (*C. albicans* and *S. cerevisiae*) with MIC 0.4-400 μg/ml.



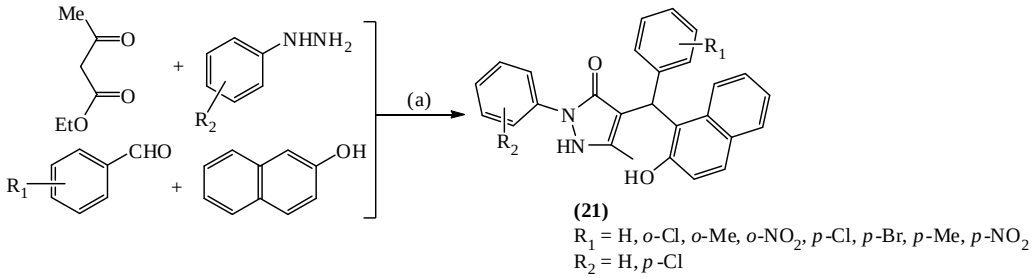
Scheme-12. Synthesis of *N*-aryl 4-aryledine pyrazolones (19): (a) Et_3N, EtOH, reflux

Earlier studies have been reported that halogenated pyrazolones are useful synthetic intermediates for synthesis of dyes [36] fused- and spiro-heterocyclic compounds [37, 38]. Brominated pyrazolones can be synthesized using Br_2-acetic acid, Br_2-water and *N*-bromosuccinimide (NBS) [39-41]. Huang *et al.* synthesized di-bromopyrazolones **(20)** using pyrazolone or hydroxypyrazolones and *N*-bromobenzamide with product yield ≥ 90% (**Scheme-13**) [42].



Scheme-13. Synthesis of dibromopyrazolones (20)

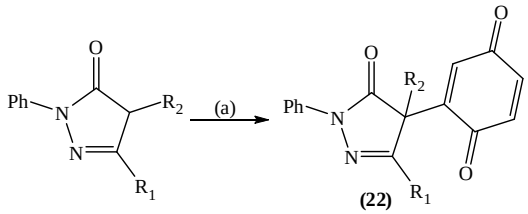
Ziarati *et al.* reported a novel green method for synthesis of *N*-arylpyrazolones (**21**) using CuI nanoparticles catalyzed four-component reaction under sonication (**Scheme-14**) [43]. Under optimized reaction conditions the yield of product was found to be 86-93%.



(21)
R_1 = H, *o*-Cl, *o*-Me, *o*-NO_2, *p*-Cl, *p*-Br, *p*-Me, *p*-NO_2
R_2 = H, *p*-Cl

Scheme-14. Four-component synthesis of pyrazolones: (a) EtOH/H_2O, ultrasound irradiation, rt, 35-40 min

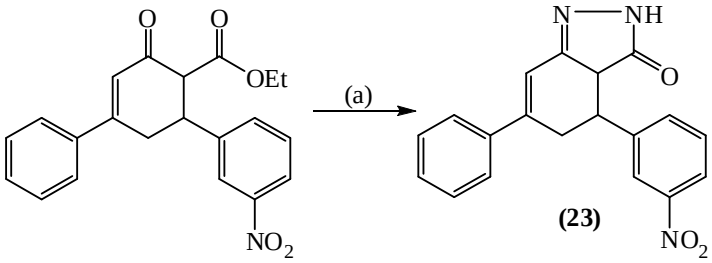
He *et al.* reported enantioselective synthesis of *p*-benzoquinone substituted pyrazolones (**22**) using cinchona alkaloid, quinine, catalyzed Michael addition/oxidation reaction with yield up to72% (99% ee), **Scheme-15** [44].



(22)
R_1 = Me, Ph, p-BrPh, p-MePh, 2-Naphthyl, 2-Thienyl
R_2 = Et, Allyl, Propargyl, Bn, (*p*-F)Bn, (*p*-Me)Bn, (*p*-MeO)Bn, (*p*-CF_3)Bn, 2-Thienylmethyl

Scheme-15. Synthesis of benzoquinone substituted pyrazolones: (a) Quinine (2 mol %), DCE, 25 °C, 24 h

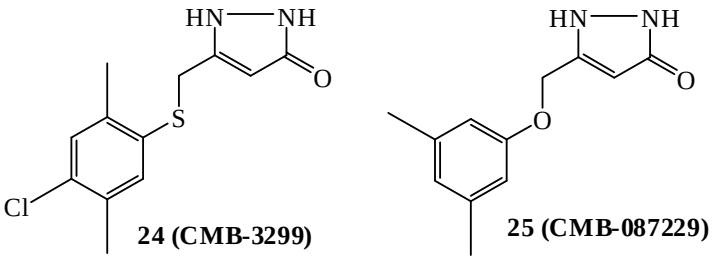
Mazimba *et al.* reported synthesis of fused-ring pyrazolones (**23**) from ethyl 2-oxocyclohex-3-enecarboxylate and hydrazine hydrate in the presence of a base with yield 70-78% (**Scheme-16**) [45]. These compounds have been shown good antimicrobial activity against *B. subtilis* and *C. albicans* with MIC values of 0.313-1.25 µg/ml. The compounds with *p*-OH group were found to exhibit good antioxidants and iron metal chelating properties.



(23)

Scheme-16. Synthesis of fused-ring pyrazolone (23): (a) $NH_2NH_2.H_2O$, Base

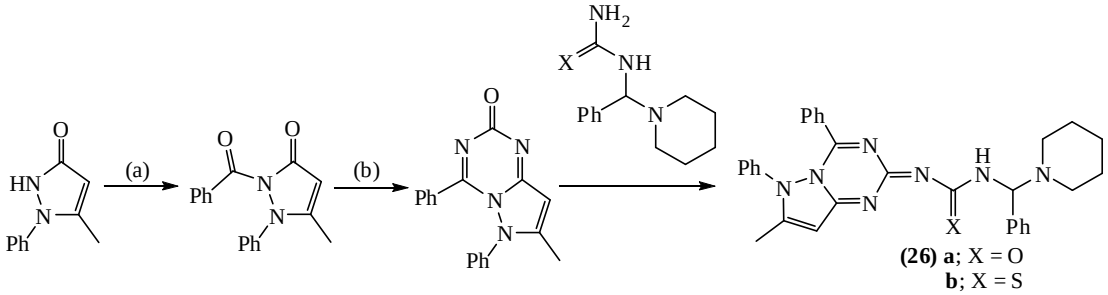
In a study Trippier *et al.* reported that pyrazolones (**24** and **25**) have therapeutic potential in amyotrophic lateral sclerosis (ALS) through activation of proteasome pathway [46]. On biological evaluation, compound **24** was found to be highly potent against ALS with EC_{50} 0.07 µM.



24 (CMB-3299) **25 (CMB-087229)**

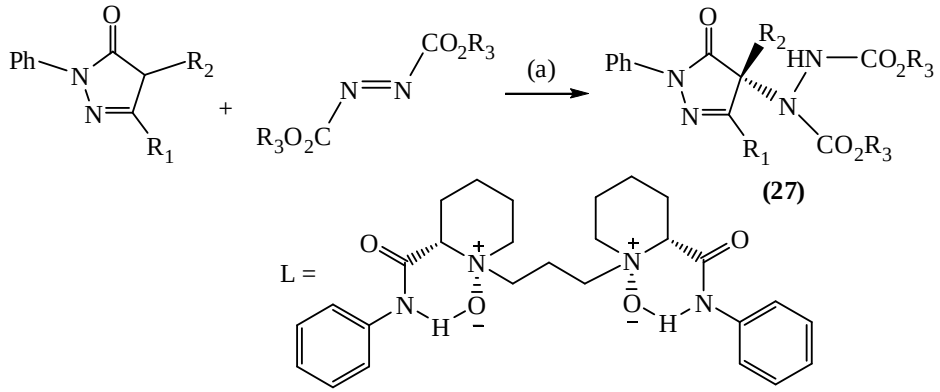
Figure-3. Structures of Anti-ALS pyrazolones (24, 25)

Patel *et al.* have been synthesized the substituted pyrazolo-triazinylidene fused ring adduct of 1-(phenyl(piperidin-1-yl)methyl)urea/thiourea (**Scheme-17**) [47]. Both compounds (**26a** and **26b**) have been shown synergistic effect on CNS depression with diazepam at a dose of 0.5 mg/kg.



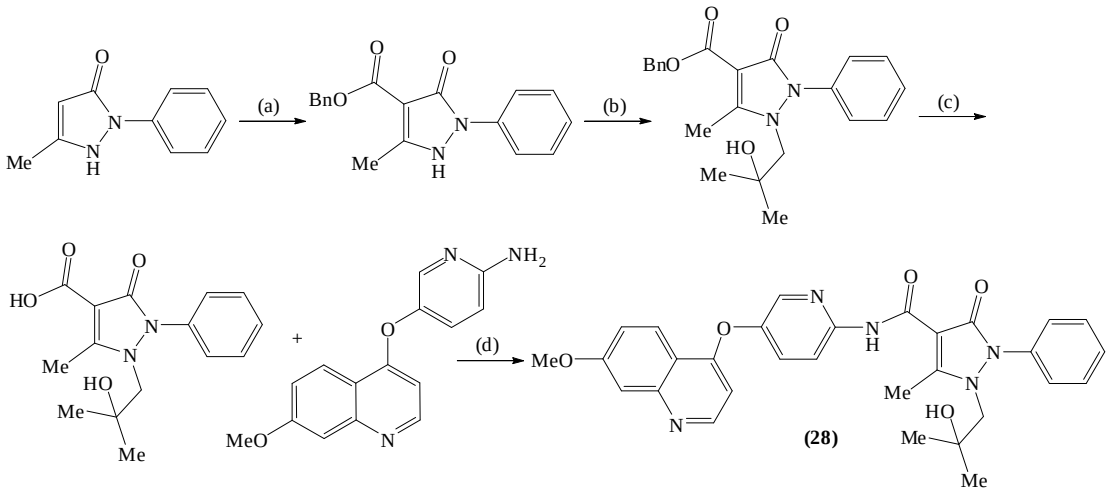
Scheme-17. Synthesis of pyrazolo-triazinylidene derivatives (26a-b)

Yang *et al.* reported synthesis of chiral 4-aminopyrazolones (**27**) from corresponding pyrazolones and azodicarboxylates using *N,N′*-dioxide gadolinium(III) complex (L-Gd(OTf)$_3$) catalyzed asymmetric α-amination (**Scheme-18**) [48].



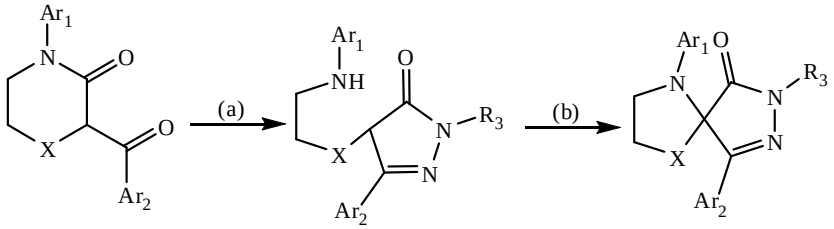
Scheme-18. Asymmetric synthesis of 4-aminopyrazolones (27): (a) L-Gd(OTf)$_3$, (0.05 or 1 mol%), 4Å MS, DCM, -20 °C

Earlier, Liu *et al.* reported novel pyrazolone derivative (**28**) as selective and highly potent orally active *c*-Met inhibitors [49]. The receptor tyrosine kinase, *c*-Met, is known as an important target for anticancer agents. Compound **28** (AMG458) showed most favorable *c*-Met based anticancer profile among the tested compounds. Synthesis of **28** was done by coupling of 4-quinolinyloxy 2-pyridinamine moiety with a pyrazolone nucleus (**Scheme-19**).



Scheme-19. Synthesis of AMG458: (a) BnCOCl, Ca(OH)$_2$, dioxane (b) 1,1-dimethyloxirane, AlMe$_3$, chlorobenzene (c) H$_2$, Pd/C, MeOH (d) HATU, (*i*Pr)$_2$EtN, DMF, 60 °C

In a study, Agejas and Ortega reported two step synthesis of spiropyrazolones (**29**) from 3-benzoyl-1-phenylpiperidin-2-ones using iodine-mediated oxidative C-N bond formation with yield of 47-93% (**Scheme-20**) [50].

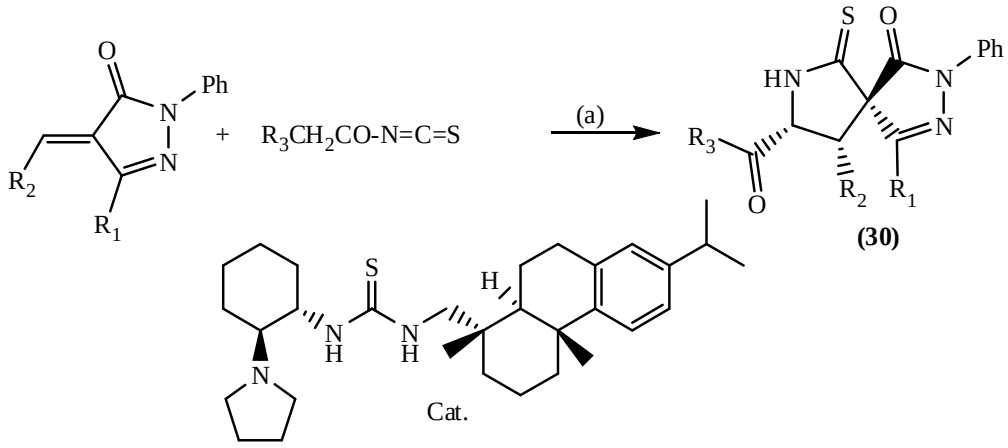


(29)
X = C, O;
Ar_1 = Ph, *o*/*m*/*p*-MePh, *p*-MeOPh, *p*-ClPh, *p*-CF_3Ph, *p*-CNPh;
Ar_2 = Et, o-MePh, m-BrPh, p-CNPh, p-MeOPh, 2-thienyl, 4-pyridyl;
R_3 = H, Ph, Bn

Scheme-20. Synthesis of spiropyrazolones (29): (a) $R_3NHNH_2.H_2O$/HCl/ 2HCl, EtOH, 75-90 °C, overnight (b) I_2, AgOTf, 0 °C, Stirring, 30-60 min

'

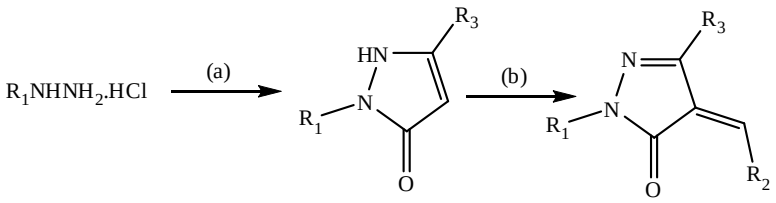
Earlier, Liu *et al.* have also reported asymmetric synthesis of pyrrolidine-2-thione-spiropyrazolones (**30**) from benzylidene pyrazolones via an organocatalytic Michael/cyclization sequence (**Scheme-21**). The reaction afforded spiropyrazolones containing three contiguous stereogenic centers with high levels of diastereo- and enantioselectivity (up to 20:1 dr and 99 % ee) [51].



(30)

Scheme-21. Synthesis of pyrrolidine-2-thione-spiropyrazolones (30): (a) Cat. (15 mol %), DCM, r.t

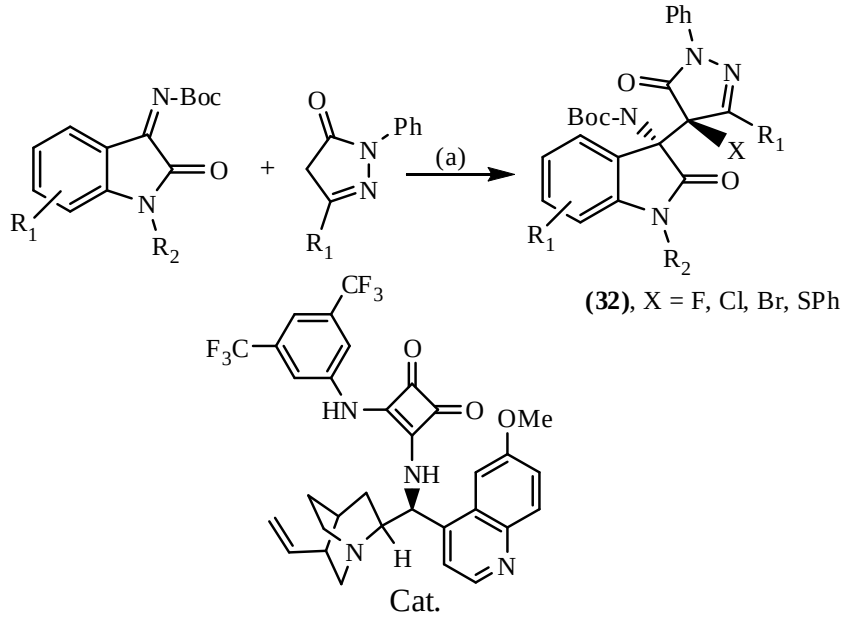
Hadi *et al.* have been reported dialkoxybenzylidene pyrazolones (**31**) as potent HIV-1 integrase inhibitors (**Scheme-22**) [52]. The SAR analysis indicated that compounds with substituents R_1 = 3,5-dichlorophenyl substituent (IC_{50} = 12±1 μM), R_2 = 3(4-fluorobenzyl) 4-methoxy benzylidene (IC_{50} = 11±1 μM) and R_3 = carboxylate (IC_{50} = 19±3 μM) having higher potency than other in strand transfer assay.



(31)
R_1= Aryl; R_2= Benzylidene; R_3 = Me, Et, CF_3, COOH

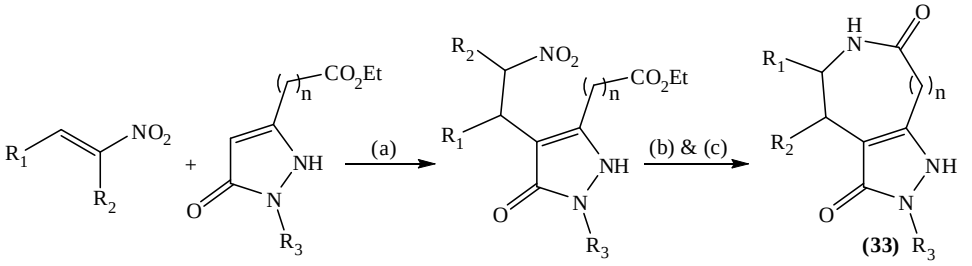
Scheme-22. Synthesis of dialkoxybenzylidene pyrazolones (31): (a) $R_3COCH_2CO_2Me$, EtOH/AcOH/K_2CO_3-EtOH, reflux (b) R_2CHO, H_2O, reflux or LiOH, MeOH/THF/H_2O

Bao *et al.* have been reported chiral synthesis of oxindole-pyrazolones (**32**) from *N*-phenylpyrazolones and isatin-derived *N*-Boc ketimines with excellent yield (92-95 %) and enantioselectivity (59-99 % ee) (**Scheme-23**) [53].



Scheme-23. Synthesis of oxindole-pyrazolones (32): (a) i. Cat. (0.5 mol %), DCM, 25 °C, ii. NFSI, K_2CO_3, DCM, 25 °C or NCS/NBS 25 °C or *N*-phenylthiophthalimide, K_2CO_3, 25 °C

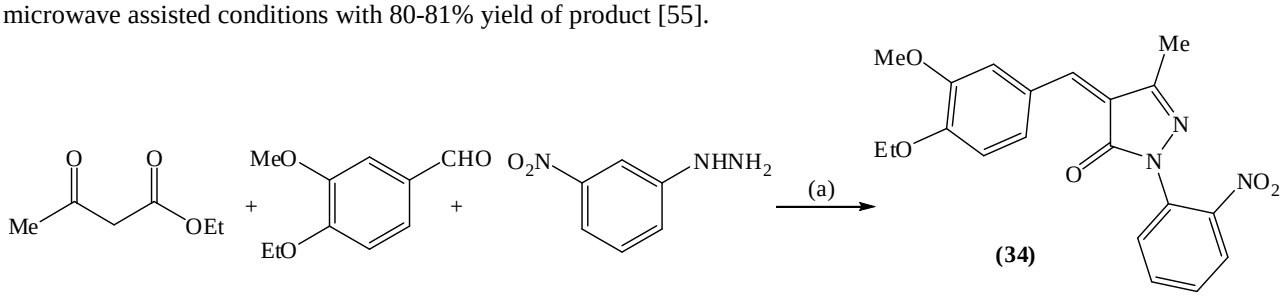
Parekh *et al.* synthesized heterocyclic-fused-pyrazolones (**33a-j**) from nitroalkenes and pyrazolo esters via DABCO-catalyzed Michael addition and reductive ring closing strategy with yield of 74-92% (**Scheme-24**) [54].



a; R_1=Ph, R_2=H R_3=Ph, n =0
b; R_1=(*p*-MeO)Ph, R_2=H, R_3=Ph, n =0
c; R_1=(*p*-$MeCO_2$)Ph, R_2=H, R_3=Ph, n =0
d; R_1=n-Pr, R_2=H, R_3=Ph, n =0
e; R_1=2-Thienyl, R_2=H, R_3=Ph, n =0
f; R_1=Ph, R_2=Me, R_3=Ph, n =0
g; R_1=R_2=1,2-Naphtho, R_3=Ph, n =0
h; R_1=Ph, R_2=H, R_3=Me, n =0
i; R_1=Ph, R_2=H, R_3=Ph, n =1
j; R_1=R_2=1,2-Naphtho, R_3=Ph, n =1

Scheme-24. Synthesis of heterocyclic-fused-pyrazolones (33a-j): (a) DABCO, DCM, r.t., 4h, (b) Zn, AcOH, r.t., 2 h, (c) Toluene : AcOH (3:2), 120 °C, 24 h

Ma *et al.* have been reported synthesis of *N*-aryl benzylidenepyrazolone (**34**) using SiO_2/Al_2O_3 under solvent free microwave assisted conditions with 80-81% yield of product [55].



Scheme-25. Synthesis of *N*-aryl benzylidenepyrazolone (34): (a) SiO_2/Al_2O_3, Solvent free, MW, 420W, 10 min

CONCLUSION

The pyrazolone is an important heterocylic skeleton that can be modified into variety of derivatives. Pyrazolone derivatives have wide scope of application, including biological activities. Several strategies have been developed to synthesize the pyrazolone derivatives for different proposes. Here, several synthetic strategies are described for development of pyrazolone derivatives along with their bio-activities. This paper will help to design novel synthetic schemes and novel pyrazolones for their possible bio-application.

Acknowledgement
The authors are thankful to Senior Dean of Lovely Faculty of Applied Medical Sciences (Lovely Professional University) for providing facilities for completion of this work.

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