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Original article

Synthesis of some novel bioactive 4-oxy/thio substituted-1*H*-pyrazol-5(4*H*)-ones via efficient cross-Claisen condensation

R. Venkat Ragavan [a,b], V. Vijayakumar [a,*], N. Suchetha Kumari [c]

[a] *Organic Chemistry Division, School of Science and Humanities, VIT University, Thiruvalam Road, Vellore 632 014, India*
[b] *Syngene International Pvt. Ltd., Biocon Park, Bangalore 560 099, India*
[c] *Department of Biochemistry, K.S. Hegde Medical Academy, Deralakatte 574162, India*

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ABSTRACT

α-Oxy/thio substituted-β-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-1*H*-pyrazol-5(4*H*)-ones by the addition of hydrazine or hydrazine derivatives and screened for their antibacterial, antifungal activities.

1. Introduction

Pyrazolone derivatives have a broad spectrum of biological activities being analgesic, antipyretic and anti-inflammatory therapeutical drugs [1–3]. Pyrazolones are also well known elicitor of hypersensitivity [4]. A class of new compounds with pyrazolone moiety was synthesized and reported for their antibacterial, antifungal activities by Al-Haiza et al. [5]. A new pyrazolone derivative, edaravone (3-methyl-1-phenyl-2-pyrazoline-5-one) is being used as a drug in clinical practice for brain ischemia [6,7] and also found to be effective against myocardial ischemia [8]. Pyrazolone derivatives such as antipyrine, aminopyrine and dipyrone are known as antipyretic and analgesic substances [9] and their pharmacological molecular mechanism has been widely surveyed. Some of the aryl oxy pyrazolone derivatives are useful in the treatment of a variety of disorders caused by Human Immunodeficiency Virus (HIV) and other genetic ailments caused by retroviruses such as Acquired Immune Deficiency Syndrome (AIDS) [10] (Fig. 1).

Herein we report the synthesis of novel pyrazolones, by introducing the oxygen or sulphur linkage at C-4 of the pyrazolone moiety and their antimicrobial evaluation. Almost all of the derivatives showed good inhibition towards bacteria and fungi.

2. Results and discussion

2.1. Chemistry

The reaction of β-keto esters with hydrazine or hydrazine derivatives is the general and most prevalent method to synthesize pyrazolones [11–15]. To synthesize pyrazolones with oxygen or sulphur linkage at the C-4 – indeed, β-keto esters with oxygen or sulphur linkage at the α-carbon are required. The reported methods to synthesis these β-keto esters have serious drawbacks such as step-intensive, time consuming and usage of imidazoles. Even though self-Claisen condensation method yields β-keto esters in single step, the main drawback is while varying substituents [16–19]. However there are a few reports on the application of cross-Claisen condensation between different esters or between esters and acid chlorides [20–24]. A nucleophilic reaction of an ester enolate with acid imidazolide has been widely used as a common method for synthesizing β-keto esters [25–28], but it can be rather expensive to use imidazolide or active ester in industrial setting. So we focused on the cross-Claisen

* Corresponding author. Tel.: +91 9443916746.
E-mail address: kvpsvijayakumar@gmail.com (V. Vijayakumar).

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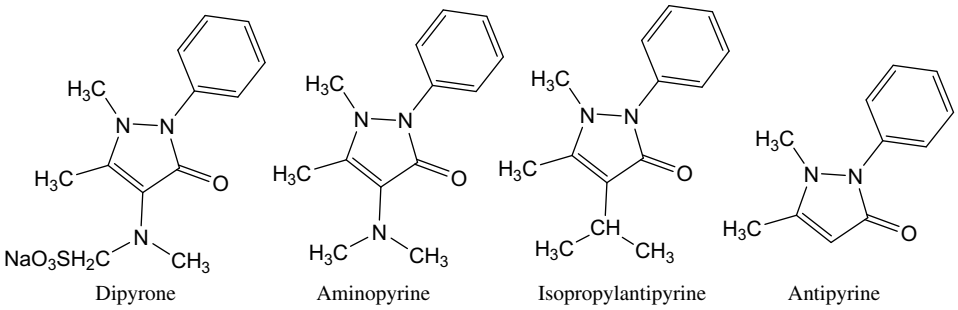


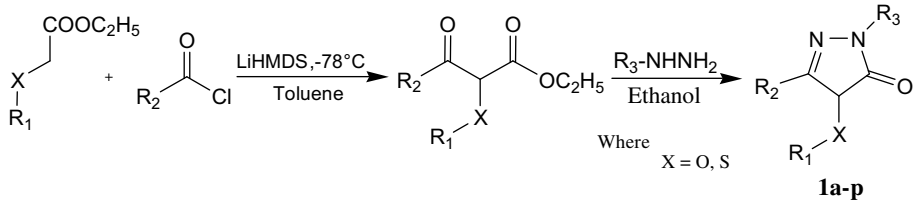
Fig. 1.

condensation between substituted oxy/thio acetic acid ethyl esters and acid chlorides to improve the yield of β-keto esters by changing the equivalence of base, acid chloride, time duration of the reaction and the mode of additions. Finally yields were improved to a greater extent in the generation of substituted aryl oxy/thio acetic acid ethyl esters and are used *in situ* to synthesize pyrazolones with oxygen or sulphur linkage at C-4 in one-pot by the addition of hydrazine or hydrazine derivatives (Scheme 1). Compounds **1a**–**n** were prepared (by Method A) from corresponding aryl oxy/thio acetic acid ethyl esters, which were synthesized (see General procedure) from their respective phenols, thiophenols, benzyl alcohol and mercaptan. When we attempted to synthesize *N*-substituted pyrazolones surprisingly substituted hydrazine like phenyl hydrazine, 4-*iso*-propyl phenyl hydrazine did not react under these conditions, which may be due to their low nucleophilicity, but strong nucleophilic hydrazine like methyl hydrazine reacted very well under these conditions. *N*-substituted pyrazolones using comparatively less nucleophilic hydrazines (**1o**–**p**) were synthesized in reasonable yield by two steps (Method B). All the synthesized compounds were characterised using ^{1}H NMR, ^{13}C NMR, LCMS and spectral data are given in Experimental section.

2.2. Pharmacology

2.2.1. Antibacterial activity

We have investigated newly synthesized pyrazolones for their antibacterial activity against *Escherichia coli* (ATTC-25922), *Staphylococcus aureus* (ATTC-25923), *Pseudomonas aeruginosa* (ATTC-27853) and *Klebsiella pneumonia* (recultured) bacterial



	X	R_1	R_2	R_3
1a	O	-Ph	$-CH_2OPh$	-H
1b	O	-Ph	$-CH_2CH_3$	-H
1c	O	-Ph	$-CH_2OCH_3$	-H
1d	O	-4-OCH_3-Ph	$-CH_3$	-H
1e	S	-Ph	$-CH_3$	-H
1f	S	-Ph	$-CH_2CH(CH_3)_2$	-H
1g	S	-Ph	$-CH(CH_3)_2$	-H
1h	S	-4-Cl-Ph	$-CH_2CH(CH_3)_2$	-H
1i	O	$-CH_2$-3-Br-Ph	$-CH_3$	-H
1j	S	$-CH_2Ph$	$-CH_2CH_3$	-H
1k	S	$-CH_2Ph$	$-CH_2OCH_3$	-H
1l	O	-Ph	-4-Cl-Ph	-H
1m	O	-Ph	$-C(CH_3)_3$	-H
1n	O	-Ph	$-CH_2CH(CH_3)_2$	$-CH_3$
1o	S	-Ph	$-CH_2CH(CH_3)_2$	-4-F-Ph
1p	O	-Ph	$-CH_2CH_3$	-4-F-Ph

Scheme 1. Synthesis of 4-oxy/thio substituted pyrazolones via cross-Claisen condensation.

strains by the disc diffusion method [29,30]. The discs measuring 6.25 mm in diameter were punched from Whatman No. 1 filter paper. Batches of 100 discs were dispensed to each screw-capped bottle and sterilized by dry heat at 140 °C for an hour. The test compounds were prepared with different concentrations using Dimethylformamide (DMF). One milliliter containing 100 times the amount of chemical in each disc was added to each bottle, which contains 100 discs. The discs of each concentration were placed in triplicate in a nutrient agar medium separately seeded with fresh bacteria. The incubation was carried out at 37 °C for 24 h. Solvent and growth controls were kept, the zones of inhibition and minimum inhibitory concentrations (MIC) were noted. Results of these studies are given in Table 1, and compared with the standard ciprofloxacin. Interestingly almost all these compounds exhibited good antibacterial activity. Among the compounds, **1a**, **1f**, **1b**, **1j**, **1g** and **1m** showed good inhibition towards all the four bacteria tested. The structure–activity relationship studies reveal that the compounds with aliphatic substituent at C-3 and free NH at N-1 (**1a**, **1b**, **1f**, **1g**, **1j** and **1m**) are very much active, the presence of methoxyl group either at aryl ring or alkyl chain reduces the antibacterial activity. Nitrogen substituted pyrazolones (either aryl or alkyl) also showed very good antibacterial activity towards *S. aureus*, *P. aeruginosa* and *K. pneumonia* but these nitrogen substituted pyrazolones are moderately active against *E. coli*. Aryl substituent at C-3 of the pyrazolones reduces the antibacterial activity against *P. aeruginosa*, *K. pneumonia* and moderately active against *E. coli* and active against *S. aureus*. Since almost all the compounds are effective, there is a need for further studies.

2.2.2. Antifungal activity

Newly synthesized pyrazolones were screened for their antifungal activity against *Aspergillus flavus* (NCIM No. 524), *Aspergillus fumigates* (NCIM No. 902), *Candida albicans* (NCIM No. 3100), *Penicillium marneffei* (recultured) and *Trichophyton mentagrophytes* (recultured) in DMSO by serial plate dilution method [16–18]. Sabouraud's agar media were prepared by dissolving peptone (1 g), D-glucose (4 g) and agar (2 g) in distilled water (100 ml) and the pH was adjusted to 5.7. Normal saline was used to make a suspension of spores of fungal strain for lawning. A loopful of particular fungal strain was transferred to 3 ml of saline to get a suspension of corresponding species. 20 ml of agar media was poured into each Petri dish. An excess of suspension was decanted and the plates were dried by placing them in an incubator at 37 °C for 1 h. Using an agar punch, wells were made on these seeded agar plates, and 10–50 μg/ml of the test compounds in DMSO was added into each well with labelling. A control was also prepared for plates in the same way using solvent DMSO. The Petri dishes were prepared in triplicate and maintained at 37 °C for 3–4 days. Antifungal activity was determined by measuring the inhibition zone. The results of these studies are given in Table 2 and compared with the standard Ciclopiroxolamine. Almost all these synthesized pyrazolones showed good activity against all the fungi tested. Particularly compounds **1a–c**, **1e–g**, **1i**, **1j** and **1m–p** were active against all the above fungi. The structure–activity relationship studies revealed that aliphatic substituent at C-3, aryl oxy/aryl thio at C-4, either substituted or free NH at N-1 may be the cause for their effectiveness against these fungi. On the other hand the methoxy substituent either at aryl ring or alkyl chains is not found to be effective against these organisms even at the higher concentrations.

Table 1
Antibacterial activities of the compounds **1a–p** (zone of inhibition in mm, MIC in mg/ml given in parenthesis).

Product	*S. aureus*	*E. coli*	*P. aeruginosa*	*Klebsiella* sp.
1a	18 (6.25)	17 (6.25)	16 (6.25)	19 (6.25)
1b	19 (6.25)	18 (6.25)	20 (6.25)	16 (6.25)
1c	17 (6.25)	12 (25)	17 (6.25)	20 (6.25)
1d	19 (6.25)	11 (25)	<10 (50)	<10 (50)
1e	18 (6.25)	13 (25)	19 (6.25)	16 (6.25)
1f	19 (6.25)	21 (6.25)	18 (6.25)	21 (6.25)
1g	20 (6.25)	18 (6.25)	17 (6.25)	16 (6.25)
1h	18 (6.25)	11 (25)	17 (6.25)	16 (6.25)
1i	21 (6.25)	11 (25)	18 (6.25)	19 (6.25)
1j	16 (6.25)	17 (6.25)	20 (6.25)	17 (6.25)
1k	17 (6.25)	<10 (50)	<10 (50)	<10 (50)
1l	21 (6.25)	12 (25)	<10 (50)	<10 (50)
1m	16 (6.25)	18 (6.25)	20 (6.25)	18 (6.25)
1n	19 (6.25)	12 (25)	19 (6.25)	17 (6.25)
1o	19 (6.25)	13 (25)	20 (6.25)	19 (6.25)
1p	16 (6.25)	14 (25)	18 (6.25)	20 (6.25)
Ciprofloxacin	23 (6.25)	32 (6.25)	28 (6.25)	24 (6.25)

Table 2
Antifungal activities of the compounds **1a–p** (Zone of inhibition in mm, MIC in mg/ml given in parenthesis).

Product	Trichophyton	Penicillium	*A. flavus*	*A. fumigates*
1a	19 (6.25)	18 (6.25)	20 (6.25)	21 (6.25)
1b	16 (6.25)	18 (6.25)	21 (6.25)	17 (6.25)
1c	17 (6.25)	17 (6.25)	18 (6.25)	20 (6.25)
1d	<10 (50)	<10 (50)	<10 (50)	<10 (50)
1e	18 (6.25)	21 (6.25)	16 (6.25)	17 (6.25)
1f	21 (6.25)	18 (6.25)	18 (6.25)	18 (6.25)
1g	16 (6.25)	19 (6.25)	18 (6.25)	20 (6.25)
1h	19 (6.25)	20 (6.25)	18 (6.25)	17 (6.25)
1i	20 (6.25)	18 (6.25)	19 (6.25)	18 (6.25)
1j	17 (6.25)	19 (6.25)	17 (6.25)	17 (6.25)
1k	<10 (50)	<10 (50)	<10 (50)	<10 (50)
1l	<10 (50)	<10 (50)	<10 (50)	<10 (50)
1m	19 (6.25)	21 (6.25)	16 (6.25)	18 (6.25)
1n	18 (6.25)	19 (6.25)	18 (6.25)	16 (6.25)
1o	18 (6.25)	19 (6.25)	20 (6.25)	19 (6.25)
1p	21 (6.25)	17 (6.25)	19 (6.25)	21 (6.25)
Ciclopiroxolamine	27 (3.125)	23 (6.25)	27 (3.125)	26 (6.25)

3. Conclusion

A series of novel pyrazolones having aryl oxy/thio substituent at the C-4 position were synthesized through efficient cross-Claisen condensation and screened for their biological activities. Almost all compounds showed good activity against all the bacteria and fungi tested. Compounds **1a**, **1b**, **1f**, **1g**, **1j** and **1m** showed the best activities against all the bacteria tested. Compounds **1a–c**, **1e–g**, **1i**, **1j** and **1m–p** showed very good activity against all the fungi tested. Alkyl groups at the C-3 of the pyrazolones increased their biological activities, but on the other hand aryl substituent at C-3 decreased their biological activities.

4. Experimental

4.1. General

All reagents were purchased from Aldrich and used as received. LiHMDS solutions were kept under nitrogen atmosphere after opening. Acid chlorides were freshly prepared and used. Dry toluene, acetic acid and ethanol were supplied by Spectrochem. All chemistry was performed under a nitrogen atmosphere using standard techniques. Melting points were determined by Buchi B-545 apparatus. All the NMR spectra were measured using either Bruker AMX 400 or Bruker DPX

300 instrument with 5 mm PABBO BB-1H tubes. ^{1}H NMR spectra were measured for approximately 0.03 M solutions in d_6-DMSO at 300 MHz or 400 MHz with TMS as internal reference. ^{13}C NMR spectra were measured for approximately 0.05 M solutions in d_6-DMSO at 75 MHz or 100 MHz with TMS as internal reference. In all the cases pyrazolone was recorded in the enol form. LCMS were obtained using Agilent 1200 series LC and Micromass zQ spectrometer. Column chromatography was performed using a Silica gel (230–400 mesh).

4.2. General procedure to synthesize aryl oxy/thio acetic acid ethyl esters (except **1i–k**)

To the solution of phenol (10 mmol) in DMF (20 ml), anhydrous K_2CO_3 (20 mmol) was added at room temperature (RT). After 10 minutes ethyl bromo acetate (10 mmol) was added and stirred at RT overnight. Reaction was monitored by TLC, reaction mixture was filtered through celite and the filtrate was concentrated to get the aryl oxy/thio acetic acid ethyl esters in good yield.

4.3. General procedure to synthesize benzyl oxy/thio acetic acid ethyl esters (for **1i–k**)

To the solution of benzyl alcohol or mercaptan (10 mmol) in DMF (20 ml), sodium hydride (12 mmol, 60% in mineral oil) was added in portions at 0 °C then stirred for 30 minutes in the same temperature. Ethyl bromo acetate (12 mmol) was added slowly at 0 °C and stirred at RT for 2 h. Reaction was monitored by TLC, and the reaction mixture was quenched with saturated NH_4Cl (20 ml), extracted with ethyl acetate (2×100 ml), the combined organic layer was washed with water (2×20 ml), brine solution (1×20 ml), dried over Na_2SO_4 and evaporated to dryness. Crude was purified by column chromatography (15% Ethyl acetate in Pet. ether) to get the product in good yield.

4.4. General procedure to synthesize 4-aryl oxy/thio-1H-pyrazol-5(4H)-ones (Method A)

LiHMDS (11 mmol, 1 M solution in THF) was added quickly via syringe to the solution of an ester (5.5 mmol) in toluene (15 ml) at −30 °C with stirring and the formed anion was allowed to stand approximately for 2 minutes then acid chloride (6.9 mmol) was added in one portion with stirring. Reaction mixture (RM) was removed from acetone–dry ice bath and the stirring continued for 10 minutes at RT, then 2 ml of acetic acid, followed by 15 ml of ethanol and hydrazine hydrate (44 mmol) were added and refluxed for 10 minutes. Then the RM was concentrated under reduced pressure, the resulting solid was dissolved in ethyl acetate, washed with brine solution, dried over Na_2SO_4 and evaporated to dryness. See specific compounds for purification details. (Methyl hydrazine was used in place of hydrazine hydrate in the preparation of compound **1n**.)

4.4.1. 3-(Benzyloxy)-4-phenoxy-1H-pyrazol-5(4H)-one (**1a**)

Purified by recrystallisation using ethanol as solvent, pale yellow solid, 89% yield, m.p. 173.8–175.1 °C, ^{1}H NMR (400 MHz, d_6-DMSO): δ 12 (br s,1H), 10 (br s, 1H), 7.22 (m, 4H), 6.88 (m, 6H), 4.81(s, 2H), ^{13}C NMR (400 MHz, d_6-DMSO): δ 159.0, 158.3, 129.8, 129.8, 122.2, 121.4, 115.4, 115.0, 59.2.

4.4.2. 3-Ethyl-4-phenoxy-1H-pyrazol-5(4H)-one (**1b**)

Purified by column chromatography (Acetone: ethyl acetate, 1:4), white solid, 42% yield, m.p. 195.3–196.8 °C, ^{1}H NMR (400 MHz, d_6-DMSO): δ 11.3 (s, 1H), 9.7 (s, 1H), 7.27 (t, $J = 15.5$ Hz, 2H), 6.96 (t, $J = 15.28$ Hz, 1H), 6.84 (d, $J = 8.56$ Hz, 2H), 2.35 (q, $J = 22.8$ Hz, 2H), 1.03 (t, $J = 15.2$ Hz, 3H); ^{13}C NMR (75 MHz, d_6-DMSO): δ 159.3, 152.9, 136.2, 130.2, 121.8, 119.9, 115.1, 17.4, 13.0; MS calcd. for $C_{11}H_{12}N_2O_2$: 204.22. Found: 205.3 (M + 1).

4.4.3. 3-Methoxymethyl-4-phenoxy-1H-pyrazol-5(4H)-one (**1c**)

Purified by column chromatography (Methanol:Ethyl acetate, 1:99), pale yellow solid, 41% yield, m.p. 145.8–146.8 °C, ^{1}H NMR (400 MHz, d_6-DMSO): $\delta = 11.70$ (br s, 1H), 9.80 (br s, 1H), 7.27 (t, $J = 7.40$ Hz, 2H), 6.97 (t, $J = 7.32$ Hz, 1H), 6.87 (d, $J = 8.60$ Hz, 2H), 4.16 (s, 2H), 3.15 (s, 3H); ^{13}C NMR (75 MHz d_6-DMSO): $\delta = 159.1$, 152.3, 131.3, 129.7, 122.0, 121.3, 115.2, 62.8, 57.76. MS calcd. for $C_{11}H_{12}N_2O_3$: 220.22. Found: 221.1 (M + 1).

4.4.4. 4-(4-Methoxyphenoxy)-3-methyl)-1H-pyrazol-5(4H)-one (**1d**)

Purified by column chromatography (Methanol:Ethyl acetate, 1:99), white solid, 47% yield, m.p. 200.6–201.5 °C, ^{1}H NMR (300 MHz, d_6-DMSO): $\delta = 11.20$ (br s, 1H), 9.70 (br s, 1H), 6.25 (d, $J = 7.21$ Hz, 2H), 6.80 (d, $J = 6.72$ Hz, 2H), 3.67 (s, 3H), 1.90 (s, 3H); ^{13}C NMR (75 MHz, d_6-DMSO): $\delta = 154.4$, 153.1, 152.9, 130.7, 121.4, 116.0, 114.9, 55.8, 9.26. MS calcd. for $C_{11}H_{12}N_2O_3$: 220.22. Found: 220.9 (M^+).

4.4.5. 3-Methyl-4-(phenylthio)-1H-pyrazol-5(4H)-one (**1e**)

Purified by column chromatography (Methanol:Ethyl acetate, 1:9), white solid 45% yield, m.p. 292.5–293.8 °C, ^{1}H NMR (300 MHz, d_6-DMSO) $\delta = 10.00$ (br s, 1H), 7.22 (t, $J = 7.65$ Hz, 2H), 7.06 (t, $J = 7.53$ Hz, 1H), 6.96 (d, $J = 8.25$ Hz, 2H), 2.08 (s, 3H); ^{13}C NMR (100 MHz, d_6-DMSO): $\delta = 162.7$, 145.0, 139.5, 129.3, 125.2, 125.1, 87.3, 10.7. MS calcd. for $C_{10}H_{10}N_2OS$: 206.2. Found: 206.9 (M^+).

4.4.6. 3-Isobutyl-4-phenylthio-1H-pyrazol-5(4H)-one (**1f**)

Purified by column chromatography (Pet. Ether:Ethyl acetate, 1:1), white solid, 51% yield, m.p. 198.7–199.9 °C, ^{1}H NMR (400 MHz, d_6-DMSO): $\delta = 12.00$ (br s, 1H), 10 (br s, 1H), 7.22 (t, $J = 7.60$ Hz, 2H), 7.07 (t, $J = 7.20$ Hz, 1H), 6.97 (d, $J = 7.60$ Hz, 2H), 2.36 (d, $J = 7.60$ Hz, 2H), 1.85 (m, 1H), 0.90 (d, $J = 4.40$ Hz, 6H); ^{13}C NMR (100 MHz, d_6-DMSO): $\delta = 162.8$, 147.9, 139.7, 129.1, 125.2, 124.9, 87.5, 34.2, 28.2, 22.6. IR (cm^{-1}) 3061, 2954, 2866, 2591, 1590. MS calcd. for $C_{13}H_{16}N_2OS$: 248.35. Found: 248.9 (M^+).

4.4.7. 3-Isopropyl-4-phenylthio-1H-pyrazol-5(4H)-one (**1g**)

Purified by column chromatography (Pet. Ether:Ethyl acetate, 1:1), white solid, 49% yield, m.p. 216.7–217.9 °C, ^{1}H NMR (400 MHz, d_6-DMSO): $\delta = 12.00$ (br s, 1H), 10.00 (br s, 1H), 7.23 (t, $J = 7.60$ Hz, 2H), 7.07 (t, $J = 7.20$ Hz, 1H), 6.97 (d, $J = 7.60$ Hz, 2H), 2.96 (m, 1H), 1.15 (d, $J = 9.60$, 6H); ^{13}C NMR (100 MHz, d_6-DMSO): $\delta = 162.8$, 154.0, 139.8, 129.2, 125.1, 125.0, 85.6, 25.8, 21.9. MS calcd. for $C_{12}H_{14}N_2OS$: 234.3. Found: 232.80 (M^-).

4.4.8. 4-(4-Chlorophenylthio)-3-isobutyl-1H-pyrazol-5(4H)-one (**1h**)

Purified by column chromatography (Pet. ether:Ethyl acetate, 1:1), yellow solid, 53% yield, m.p. 227.8–228.9 °C, ^{1}H NMR (400 MHz, d_6-DMSO): $\delta = 12.00$ (br s, 1H), 10.00 (br s, 1H), 7.29 (d, $J = 8.40$ Hz, 2H), 6.98 (d, $J = 6.80$ Hz, 2H), 2.36 (d, 6.80 Hz, 2H), 1.85 (m, 1H), 0.78 (d, $J = 6.40$ Hz, 6H); ^{13}C NMR (100 MHz, d_6-DMSO) δ 162.7, 147.9, 138.9, 129.5, 129.1, 126.8, 87.1, 34.2, 28.2, 22.6. MS calcd. for $C_{13}H_{15}ClN_2OS$: 282.8. Found: 283.0 (M^+).

4.4.9. 4-(3-Bromobenzyloxy)-3-methyl-1H-pyrazol-5(4H)-one (**1i**)

Purified by column chromatography (Methanol:Ethyl acetate, 1:99), white solid, 40% yield, m.p. 182.9–184.0 °C, ^{1}H NMR (400 MHz, d_6-DMSO): $\delta = 10.80$ (br s, 1H), 9.60 (br s, 1H), 7.57 (s, 1H), 7.50 (d, $J = 5.91$ Hz, 1H), 7.37 (d, $J = 5.76$ Hz, 1H), 7.31

(t, $J = 7.72$ Hz, 1H), 4.81 (s, 2H), 1.90 (s, 3H); ^{13}C NMR (75 MHz. d_6-DMSO): $\delta = 152.8$, 141.2, 131.0, 130.9, 130.85, 129.4, 127.4, 125.12, 121.9, 73.9, 9.2. Found: 282.498 and 284.495. MS calcd. for $C_{11}H_{11}BrN_2O_2$: 283.12. Found: 284.8 (M + 1).

*4.4.10. 4-(Benzylthio)-3-ethyl-1*H*-pyrazol-5(4*H*)-one (**1j**)*

Purified by column chromatography (Methanol:Ethyl acetate, 1:9), off-white solid, 41% yield, m.p. 227.3–228.8 °C, ^{1}H NMR (400 MHz, d_6-DMSO): $\delta = 11.50$ (br s, 1H), 9.80 (br s, 1H), 7.25–7.08 (m, 3H), 7.07 (d, $J = 6.64$ Hz, 2H), 3.66 (s, 2H), 2.10 (q, $J = 8.00$ Hz, 2H), 0.84 (t, $J = 7.60$ Hz, 3H); ^{13}C NMR (100 MHz, d_6-DMSO): $\delta = 162.5$, 149.4, 139.1, 129.2, 128.4, 126.9, 89.4, 18.1, 13.3. MS calcd. for $C_{12}H_{14}N_2OS$: 234.3. Found: 234.9 (M^+).

*4.4.11. 4-(Benzylthio)-3-methoxymethyl-1*H*-pyrazol-5(4*H*)-one (**1k**)*

Purified by column chromatography (Pet. ether:Ethyl acetate, 1:1), pale yellow solid, 41% yield, m.p. 114.4–115.7 °C, ^{1}H NMR (400 MHz, d_6-DMSO): $\delta = 7.31$–717 (m, 3H), 7.07 (d, $J = 7.60$ Hz, 2H), 3.79 (s, 2H), 3.69 (s, 2H), 3.13 (s, 3H); ^{13}C NMR (100 MHz, CD_3OD): $\delta = 164.3$, 148.3, 140.7, 130.7, 129.7, 128.3, 93.1, 65.7, 59.0, 41.3. MS calcd. for $C_{12}H_{14}N_2O_2S$: 250.32. Found: 251.0 (M^+).

*4.4.12. 3-(4-Chlorophenyl)-4-phenoxy-1*H*-pyrazol-5(4*H*)-one (**1l**)*

Purified by column chromatography (Methanol:Ethyl acetate, 1:99), pale yellow solid, 40% yield, m.p. 207.5–208.6 °C, ^{1}H NMR (300 MHz, d_6-DMSO): $\delta = 12.20$ (br s, 1H), 10.10 (br s, 1H), 7.63 (d, $J = 8.25$ Hz, 2H), 7.45 (d, $J = 10.68$ Hz, 2H), 7.28 (t, $J = 8.04$ Hz, 2H), 6.98 (t, $J = 7.53$ Hz, 1H), 6.91(d, $J = 7.74$ Hz, 2H); ^{13}C NMR (75 MHz, d_6-DMSO): $\delta = 158.3$, 132.8, 130.1, 129.4, 126.8, 122.4. MS calcd. for $C_{15}H_{11}ClN_2O_2$: 286.71. Found: 287.2.

*4.4.13. 3-Tert-butyl-4-phenoxy-1*H*-pyrazol-5(4*H*)-one (**1m**)*

Purified by preparative HPLC, brown solid, 39% yield, m.p. 233.3–234.6 °C, ^{1}H NMR (300 MHz, d_6-DMSO): $\delta = 10.00$ (br s, 2H), 7.26 (t, $J = 7.44$ Hz, 2H), 6.94 (t, $J = 6.96$ Hz, 1H), 6.83 (d, $J = 7.53$ Hz, 2H), 1.16 (s, 9H); ^{13}C NMR (75 MHz, d_6-DMSO): $\delta = 159.0$, 153.1, 142.7, 129.8, 121.8, 119.0, 115.1, 31.7, 29.2. MS calcd. for $C_{13}H_{16}N_2O_2$: 232.27. Found: 233.3 (M + 1).

*4.4.14. 3-Isobutyl-1-methyl-4-phenoxy-1*H*-pyrazol-5(4*H*)-one (**1n**)*

Purified by column chromatography (Methanol:Dichloromethane, 2:98) pale brown solid, 41% yield, m.p. 141.2–141.9 °C, ^{1}H NMR (400 MHz, CD_3OD): $\delta = 7.27$ (t, $J = 7.48$ Hz, 2H), 6.97 (t, $J = 7.32$ Hz, 1H), 6.92 (d, $J = 7.60$ Hz, 2H), 3.48 (s, 3H), 2.31 (d, $J = 7.28$ Hz, 2H), 1.89 (m, 1H), 0.96 (d, $J = 6.28$ Hz, 6H); ^{13}C NMR (100 MHz, CD_3OD): $\delta = 160.2$, 142.7, 130.8, 123.4, 116.3, 34.9, 32.0, 29.2, 22.0. MS calcd. for $C_{14}H_{18}N_2O_2$: 246.305. Found: 247.0 (M^+).

4.5. General procedure to synthesize N*-substituted-4-aryl oxy/thio-2, 4-dihydro-pyrazol-3-ones (Method B)*

LiHMDS (11 mmol, 1 M solution in THF) was added quickly via syringe to the solution of an ester (5.5 mmol) in toluene (15 ml) at −30 °C with stirring and thus formed anion was allowed to stand approximately for 2 minutes then acid chloride (6.9 mmol) was added in one portion while stirring. Reaction mixture was removed from acetone–dry ice bath and continues the stirring for 10 minutes, then quenched with water and extracted with ethyl acetate (2 × 100 ml) and the combined organic layer was dried over anhydrous Na_2SO_4, concentrated on rotary evaporator. The above crude was taken in the mixture of ethanol (20 ml) and acetic acid (2 ml), to this substituted hydrazine (10 mmol) was added and refluxed overnight. Reaction was monitored by TLC, reaction mixture was concentrated to dryness. See specific compounds for purification details.

*4.5.1. 1-(4-Fluorophenyl)-3-isobutyl-4-phenylthio-1*H*-pyrazol-5(4*H*)-one (**1o**)*

Purified by column chromatography (30% Ethyl acetate in Pet. ether), white solid, 38% yield, m.p. 220.4–221.3 °C, ^{1}H NMR (400 MHz, d_6-DMSO): $\delta = 12.20$ (br s, 1H), 7.75 (d, $J = 8.52$ Hz, 2H), 7.28 (m, 4H), 7.08 (m, 3H), 2.35 (d, $J = 3.08$ Hz, 2H), 1.92 (m, 1H), 0.84 (d, $J = 6.56$ Hz, 6H); ^{13}C NMR (400 MHz, d_6-DMSO): $\delta = 161.5$, 159.1, 155.0, 139.0, 135.2, 129.4, 125.4, 125.3, 123.5, 116.3, 116.1, 55.4, 36.1, 27.8, 22.8. MS calcd. for $C_{19}H_{19}FN_2O_2$: 320.36. Found: 320.8 (M^+).

*4.5.2. 3-Ethyl-1-(4-fluorophenyl)-4-phenoxy-1*H*-pyrazol-5(4*H*)-one (**1p**)*

Purified by column chromatography (30% ethyl acetate in Pet. ether), white solid, 39% yield, m.p. 168.8 °C, ^{1}H NMR (400 MHz, d_6-DMSO): $\delta = 11.58$ (br s, 1H), 7.75 (d, $J = 8.80$ Hz, 2H), 7.32 (t, $J = 7.20$ Hz, 3H), 7.00 (m, 3H), 2.34 (br s, 2H), 1.60 (br s, 3H); ^{13}C NMR (400 MHz, d_6-DMSO): $\delta = 158.8$, 146.3, 135.9, 130.1, 123.1, 122.3, 119.2, 166.2, 116.0, 115.5, 115.2, 19.8, 12.5. MS calcd. for $C_{17}H_{15}FN_2O_2$: 298.31. Found: 298.6 (M^+).

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Appendix. Supplementary data

Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.ejmech.2009.04.010.

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