FREE RADICAL SCAVENGING PROPERTY OF 4-OXY/THIO SUBSTITUTED-1*H*-PYRAZOL-5(4*H*)-ONES

R. Venkat Ragavan[1], V. Vijayakumar[1,*], N. Suchetha Kumari[2]

[1]*Organic Chemistry Division, School of Advanced Sciences, VIT University, Vellore 632 014, India.*
[2]*Department of Biochemistry, K.S. Hegde Medical Academy, Deralakatte 574 162, India.*

Correspondence Author
V. Vijayakumar
E mail: kvpsvijayakumar@gmail.com;
Contact: +91-416-2202535

Summary

A series of 4-Oxy/thio substituted-1*H*-pyrazol-5(4*H*)-ones **1-27** were subjected to free radical scavenging property by DPPH method and almost all the compounds found to have good scavenging activity compared to the standards Ascorbic acid and Curcumin.

Keywords*:* 4-Oxy/thio substituted-1*H*-pyrazol-5(4*H*)-ones; anti-oxidant property; DPPH method.

Introduction

Among the family of heterocycles, nitrogen containing heterocycles especially pyrazoles is an important class of heterocycles and its derivatives are reported to have the broad spectrum of biological activities such as antiinflammatory [1-2], herbicidal [3] and antiviral [4-5]. Pyrazole derivatives are extensively studied and used as antimicrobial agents [6-11]. It also acts a radical scavenger to interrupt the peroxidative chain reactions and membrane disintegrations associated with ischemia [12-14] As part of our on-going research aiming the synthesis of new antimicrobial compounds, new derivatives of pyrazol-5(4*H*)-ones have been synthesised and reported in literature by us with modified methodology [15-17]. In continuation of our earlier work here in we report the antimicrobial evaluation of some of these 4-Oxy/thio substituted-1*H*-pyrazol-5(4*H*)-ones.

Materials and methods

Chemistry

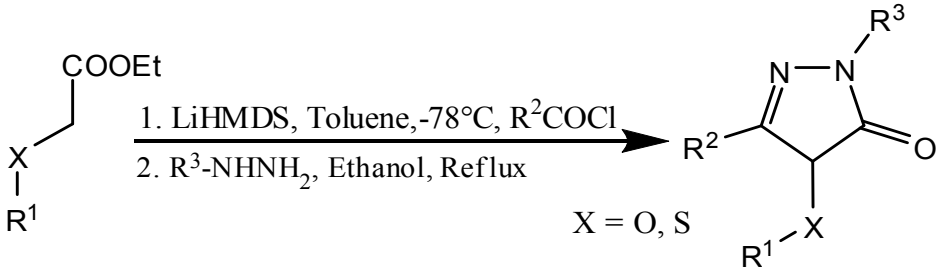
The 4-Oxy/thio substituted-1*H*-pyrazol-5(4*H*)-ones **1-15** were synthesised using the method available in literature [17].

Anti-oxidant evaluation:

Antioxidant properties of the newly synthesized compounds were studied by the DPPH (Diphenyl picryl hydrazyl) assay method [18]. The ability of compounds towards DPPH radical scavenging was carried out by mixing 0.1mM solution of DPPH and the specific concentration of each sample. After 10 min. reaction time the samples were observed spectrophotometrically at 517 nm, and the DPPH radical scavenging ability was compared with the standards curcumin and ascorbic acid. Antioxidant properties of each compound by DPPH assay was carried out at three different concentrations (0.5 mL, 1.0 mL and 1.5 mL) of each sample and tabulated in Table-2.

Results and Discussion

A series of 4-oxy/thiosubstituted-1*H*-pyrazol-5(4*H*)-ones **1-15** were synthesised (Scheme 1), using the procedure already reported by us in literature [15,17] and then subjected to the preliminary anti-oxidant studies and those results given Table-2.



Scheme 1 Synthesis of pyrazolones by cross-Claisen condensation

The results in Table 2 reveal that almost all the compounds have shown the good free radical scavenging ability under the tested conditions. Interestingly compounds **1-5, 7, 9-13, 17-20, 22-26** were exhibited higher DPPH radical scavenging activity than standard Ascorbic acid. Compounds **14** and **16** were equipotent as standard Ascorbic acid. Compounds **15, 21** and **27** were very poor radical scavengers. Surprisingly compounds **4, 12, 13** and **19** have shown the very good DPPH radical scavenging activity than the standard curcumin. On the other hand compounds **1-5, 7, 9, 10, 18, 20, 22-24** were equally active as standard curcumin. SAR studies reveals that compounds having both alkyl (methyl) and aryl (4-methoxyphenyl, 4-cyanophenyl, benzyl, 3-bromobenzyl) linked by either oxygen or sulphur to the C-4 of the pyrazolone is active than the standard. Substitutions at the N-1 did not do many changes on the activity. Aliphatic chains (*n*-pentyl, *iso*-butyl, *iso*-propy propyl) at C-3 of the pyrazolone ring decrease the antioxidant property. Since almost all the compounds were active there is a need of further studies.

Table-1 Various 4-oxy/thiosubstituted-1*H*-pyrazol-5(4*H*)-ones.

Product	X	R^1	R^2	R^3	Yield(%)[a]
1	O	-Ph	$-CH_3$	-H	64
2	O	$-CH_3$	-4Cl-Ph	-H	57
3	O	$-CH_2$-3Br-Ph	$-CH_2CH_3$	-H	60
4	O	$-4OCH_3$-Ph	$-CH_2CH_3$	-H	57
5	O	-4CN-Ph	$-CH_3$	-H	48

6	S	-Ph	- $(CH_2)_4CH_3$	-H	74
7	S	-CH_2Ph	-Cyclopropyl	-H	54
8	S	-4Cl-Ph	-Ph	-H	52
9	O	-Ph	-CH_2CH_3	-H	57
10	O	-Ph	-CH_2OCH_3	-H	54
11	O	-CH_2-3Br-Ph	-CH_3	-H	58
12	O	-4OCH_3-Ph	-CH_3	-H	62
13	S	-Ph	-CH_3	-H	67
14	S	-Ph	-Isobutyl	-H	74
15	S	-Ph	-CH $(CH_3)_2$	-H	71
16	S	-CH_2Ph	-CH_2CH_3	-H	61
17	S	-CH_2Ph	-CH_2OCH_3	-H	58
18	S	-4Cl-Ph	-Isobutyl	-H	78
19	O	-Ph	-4Cl-Ph	-H	59
20	O	-Ph	-$C(CH_3)_3$	-H	58
21	O	-Ph	-Isobutyl	-CH_3	64
22	O	-Ph	-CH_2CH_3	-CH_3	77[c]
23	S	-Ph	-CH_3	-4F-Ph	58[d]
24	O	-Ph	-CH_3	-4F-Ph	60[d]
25	S	-Ph	-Isobutyl	-4F-Ph	51[d]
26	O	-Ph	-CH_2CH_3	-4F-Ph	61[d]
27	S	-Ph	- $(CH_2)_4CH_3$	-2-pyridyl	29[c,d]

Percentage of antioxidant activity was calculated as follows
The percentage of DPPH remaining was calculated according to the equation:
$\%\ DPPH_{REM} = [DPPH]_{(t)} / [DPPH]_{(0)} \times 100$
Where $[DPPH]_{(0)}$ is its remaining concentration of the stable radical without the antioxidant and $[DPPH]_{(t)}$ is its remaining concentration at the reaction plateau step.
% Antioxidant Activity (AA) = 100 - $\%\ DPPH_{REM}$

Table-2 Antioxidant study of newly synthesized compounds by DPPH assay method[a]

Product	volume of compound taken for assay (200µg/mL concentration)		
	0.5 mL	1.00 mL	1.5 mL
322	58.33%	64.28%	79.57%
323	54.87	60.72	66.49%
324	59.55	67.38	71.23
325	49.21	57.17	63.29
326	57.77	65.28	70.00
327	25.75	45.45	53.00
328	43.36	46.90	56.63
330	15.92	22.12	29.63
332	57.00	62.13	78.66
333	58.65	64.67	80.13
334	44.31	54.87	56.79
335	63.10	69.28	74.13

336	71.21	75.75	81.81
337	21.23	28.61	30.17
338	9.25	26.00	49.07
339	32.40	37.96	50.92
340	49.90	56.63	61.21
341	51.32	56.63	55.12
342	59.03	71.42	85.71
343	55.12	60.39	70.21
344	8.33	10.82	17.89
348	56.43	73.20	81.18
350	50.49	64.35	71.28
352	47.52	70.29	93.06
353	44.87	64.96	72.41
354	44.00	55.75	62.83
355	14.85	30.69	42.57
Ascorbic acid	30.63	39.26	49.22
Curcumin	53.22	61.11	76.08

[a]concentration of DPPH is 0.1mM

References

1. Singh SP, Prakash O, Tomer RK, Sawhney SN, Synthesis and anti-inflammatory activity of some 2-(3'-aryl-5'-amino-1'-pyrazolyl)benzothiazoles and benzimidazoles, *Indian J Chem.,* 1978; 16B: 733-735.
2. Tewari AK, Mishra A, Synthesis and anti-inflammatory activities of N^4, N^5-disubstituted-3-methyl-1H-pyrazolo[3,4-c]pyridazines, *Bioorg Med Chem.,* 2001; 9: 715-718.
3. Kudo N, Furuta S, Taniguchi M, Endo T, Sato K, Synthesis and Herbicidal Activity of 1,5-Diaryl pyrazole Derivatives, *Chem Pharm Bull.,* 1999; 47: 857-868.
4. Storer R, Ashton CJ, Baxter AD, Hann MM, Marr CLP, Mason AM, Mo CL, Myers PL, Noble SA, Penn CR, Weir NG, Woods JM, Coe PL, The Synthesis and Antiviral activity of 4-Fluoro-1-β-D-ribofuranosyl-1*H*-pyrazole-3-carboxamide, *Nucleosides Nucleotides and Nucleic acids*, 1999; 18: 203-216.
5. Genin MJ, Biles C, Keiser BJ, Poppe SM, Swaney SM, Tarpley WG, Yagi Y, Romero DL, Novel 1, 5-Diphenyl pyrazole Nonnucleoside HIV-1. Reverse Transcriptase inhibitors with Enhanced Activity versus the Delaviridine-Resistant P236L mutant: Lead identification and SAR of 3-and 4-substituted derivatives, *J Med Chem.,* 2000; 43: 1034-1040.
6. Tanitame A, Oyamada Y, Ofuji K, Fujimoto M, Suzuki K, Ueda T, Terauchi H, Kawasaki M, Nagai K, Wachi M, Yamagishi J, Synthesis and antibacterial activity of novel and potent DNA gyrase inhibitors with azole ring, *J Bioorg Med Chem.,* 2004; 12: 5515-5524.
7. Tanitame A, Oyamada Y, Ofuji K, Terauchi H, Kawasaki M, Wachi M, Yamagishi J, Synthesis and antibacterial activity of novel series of DNA gyrase inhibitors: 5-[(E)-2-arylvinyl]pyrazoles, *Bioorg Med Chem Lett.,* 2005; 15: 4299-4303.
8. Kane JL (Jr.), Hirth BH, Liang B, Gourlie BB, Nahill S, Barsomian G, Ureas of 5-aminopyrazole and 2-aminothiazole inhibit growth of gram-positive bacteria, *Bioorg Med Chem Lett.,* 2003; 13: 4463-4466.

9. Menozzi TG, Merello L, Fossa P, Schenone S, Ranise A, Mosti L, Bondavalli F, Loddo R, Murgioni C, Mascia V, La Colla P, Tamburini E, Synthesis, antimicrobial activity and molecular modeling studies of halogenated 4-[1H-imidazoles-1-yl(phenyl)methyl]1,5-diphenyl-1*H*-pyrazoles, *Bioorg Med Chem.,* 2004; 12: 5465-5483.
10. Bekhit AA, Fahmy HTY, Rostom SAF, Baraka AM, Design and synthesis of some substituted-1*H*-pyrazolyl-thiazolo[4,5-d]pyrimidines as anti-inflammatory-antimicrobial agents, *Eur J Med Chem.,* 2003; 38: 27-36.
11. Akbas E, Berber I, Antibacterial and antifungal activities of new pyrazolo[3,4-d] pyridazine derivatives, *Eur J Med Chem.,* 2005; 40: 401-405.
12. Kawai H, Nakai H, Suga M, Yuki S, Watanabe T, Saito KI, Effects of a novel Free Radcal scavenger, MCI-186, on Ischemic Brain Damage in the Rat Distal middle Cerebral Artery occlusion model, *J Pharmcol Exp Ther.,* 1997; 281: 921-927.
13. Watanabe T, Yuki S, Egawa M, Nishi H, Protective effects of MCI-186 on cerebral ischemia: posible involvement of free radical scavenging and antioxidant actions, *J Pharmacol Exp Ther.* 1986; 268: 1597-1604.
14. Wu TW, Zeng LH, Wu J, Fung KP, Myocardial protection of MCI-186 in rabbit ischemia-reperfusion, *Life Sci*., 2002; 71: 2249-2255.
15. Venkat Ragavan R, Vijayakumar V, Suchetha Kumari N, Synthesis of some novel bioactive 4-oxy/thio substituted-1*H*-pyrazol-5(4*H*)-ones via efficient cross-Claisen condensation, *Eur J Med Chem.,* 2009; 44: 3852-3857.
16. Venkat Ragavan R, Vijayakumar V, Suchetha Kumari N, Synthesis and antimicrobial activities of novel 1,5-diaryl pyrazoles, *Eur J Med Chem.,* 2010; 45: 1173-1180.
17. Venkat Ragavan R, Vijayakumar V, A Novel Route to 4-Oxy/thio substituted-1H-pyrazol-5(4H)-ones via Efficient Cross-Claisen Condensation, *J Heterocyclic Chem.,* 2011; 48: 323-330.
18. Mensor LL, Menzes FS, Leitao GG, Reis AS, Dosantos TC, Coube CS and Leitao SG, Screening of Brazilian extract for antioxidant activity by the DPPH free radical method, *Phytother Res.,* 2001; 15: 127–130.