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SYNTHESIS OF N-SUBSTITUTED PYRAZOLO PYRIMIDO PYRIMIDINES AND THEIR ANTIOXIDANT EVALUATION

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ABSTRACT:
A novel series of N-substituted pyrazolo pyrimido pyrimidines synthesized by treating an equimolar quantity of 3-cyano-2-methylthio-6-methyl-4,8-dioxo-9*H*-pyrimido[1,2-*a*] pyrimidine (3) with hydrazine hydrate and its different aryl and heteryl derivatives in N,N'-dimethyl formamide (DMF) and anhydrous potassium carbonate as catalyst. All the structures were confirmed on the basis of spectroscopic and physico-chemical properties. Anti-oxidant activities of newly synthesized compounds were evaluated by using DPPH free radical model.

KEY WORDS: Pyrimidine, DMF, potassium carbonate, antioxidant activity, DPPH.

INTRODUCTION:

Pyrimidine is the base of life because it is interior part of nucleic acid components such as uracil, cytosine and thymine. It is also present in naturally occurring substances mainly vitamins like riboflavin and thiamine. Pyrimidine is the heterocyclic aromatic compound similar to benzene and pyridine containing two nitrogen atoms at 1 and 3 positions in the six membered rings. Pyrimidine having structurally two important isomeric forms such as pyrazine, an analog with the nitrogen atoms in positions 1 and 4 and pyridazine, an analog with the nitrogen atoms in positions 1 and 2. Pyrazolo-pyrimido-pyrimidine containing three fused heterocyclic ring in a single molecule shows remarkable biological and pharmacological properties such as antimicrobial[1], antidiabetic[2], anti-HIV[3], antimalerial[4], anticonvulsants[5], antifungal[6], antiviral[7], anti-tumor[8], antiinflammatory[9].
Tarik et al[10] reported the synthesis of pyrazolo pyrido pyrimidine by refluxing pyrazolo pyridine in formic acid. Synthesis of pyrazolo pyrido pyrimidine has been described by reacting o-aminoaldehyde with amides by Sandeep M. Bagal et al[10]. Sambhaji et al[11] reported the synthesis of 7-bromo-3-cyano-4-imino-2-methylthio-4*H*-pyrido[1,2-a]pyrimidines and its hydrazino derivatives. Study of reported literature reveals that not enough work has been done on the synthesis of pyrimido pyrimidine fused with hydrazine derivatives.

In the present study, we reported a novel series of N-substituted pyrazolo pyrimido pyrimidine derivatives and evaluate their anti-oxidant activity.

MATERIAL AND METHODS:

All the chemicals used in present works are from analytical grade and used without further purification. Melting points of the products were determined in open capillary tubes on an electrothermal melting point apparatus and were uncorrected. All the reactions were monitored by TLC. IR spectra were recorded on Shimadzu FT-IR spectrophotometer, ^{1}H-NMR spectra were obtained on Bruker avance spectrophotometer 500 MHz in DMSO-d6 using tetramethylsilane as an internal standard. Mass spectra were recorded on GC-MS spectrometer using the ESI technique.

DPPH (1, 1-diphenyl-2-picryl hydrazine) radical scavenging assay:

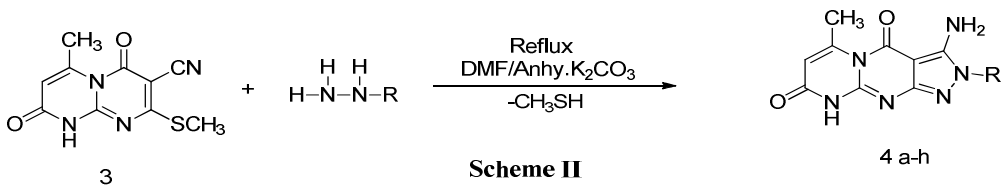
The reaction cocktail was prepared by mixing individual compounds with equivalent volume of DPPH radical (10.-4.0 M in absolute ethyl alcohol) solution. After 20 min. of reaction time, the absorbance was recorded at 517 nm using UV-Visible spectrophotometer (Blois M.S. et al 1958, Roberta R et al 2006).

Synthesis of 3-amino-6-methyl-4,8-dioxo-2-(substituted)pyrazolo[5,4-*d*]pyrimido[1,2-*a*]-9*H*-Pyrimidines (4a-h)

The mixture of compound (3) (0.01 mol) independently treated with hydrazine hydrate (80%), phenyl hydrazine, 4-nitro phenyl hydrazine, 2,4-dinitrophenyl hydrazine, 2-hydrazino benzothiazole, 6-chloro-2-hydrazinobenzothiazole, 6-nitro-2-hydrazinobenzothiazole, 6-methyl-2-hydrazinobenzothiazole,6-methoxy-2-hydrazinobenzothiazole,4,6-dimethyl-2-hydrazinobenzo thiazole(0.01mol) in 20ml of N,N'-dimethyl formamide (DMF) and anhydrous potassium carbonate (10mg) was refluxed for 4-5 hours. The reaction mixture was cooled to room temperature and poured in to ice cold water. The separated solid product was filtered, washed with water and recrystalized from ethanol to give pure **(4a-h).**

RESULT AND DISCUSSION:

In present work, we have reported one pot synthesis of 3-amino-6-methyl-4,8-dioxo-2-N-(substituted) pyrazolo[5,4-*d*]pyrimido[1,2-*a*]-9*H*-Pyrimidines(4a-h). The reactions started from 3-cyano-2-methylthio-6-methyl-4,8-dioxo-9*H*-pyrimido[1,2-*a*]pyrimidine (3) and hydrazine hydrate and their different substituted derivatives. According to these reactions compound (3) reacted with hydrazino hydrate, phenyl hydrazine, 4-nitrophenyl hydrazine, 2,4-dinitrophenylhydrazine, 2-hydrazinobenzothiazole, 6-methyl-2-hydrazino benzo thiazole,6-methoxy-2-hydrozinobenzothiazole, 6-nitro-2-hydrozinobenzothiazole to obtain 3-amino-6-methyl-4,8-dioxo-2-N-(substituted)pyrazolo[5,4-*d*]pyrimido[1,2-*a*]-9*H*-Pyrimidines(4a-h) given in scheme-II. In fact compound **(3)** having replicable active methylthio group at 2- position which is a good leaving group and stimulated due to adjacent electronegative ring nitrogen atom and electron withdrawing cyano (-CN) group.



3 **Scheme II** 4 a-h

comp.code	R	comp.code	R
4a	-H	4e	
4b		4f	
4c		4g	
4d		4h	

Spectral and physical data:

The structures of newly synthesized compounds were confirmed on the basis of spectral analysis such as IR, ^{1}HNMR, ^{13}CNMR & Mass spectral data. Compounds 4a-h, shows IR absorption band in the range of 3174 cm^{-1} to 3380 cm^{-1} due to sec amide -N-H and carbonyl sterch occurs between 1600 cm^{-1} to 1780 cm^{-1}. ^{1}H NMR is one of the very important tools for verification of organic molecules in that we observed the characteristics peaks from δ 5.29 to 5.9 ppm due to =C-H proton in all the structures. Similarly, sec amide proton shows singlet between δ 9.4 to 10.16 ppm. Molecular ion peaks of mass spectra are also in good agreement with the molecular weight of structures.

3-Amino-6-methyl-4,8-dioxo-2-N-(phenyl)pyrazolo[5,4-*d*]pyrimido[1,2-*a*]-*9H*-Pyrimidine (4b): IR: 3190 cm^{-1}, 3380 cm^{-1} (-NH,-NH$_2$), 1674 cm^{-1}(-C=O), 1600 cm^{-1} (-C=O), ^{1}H NMR : (500 MHz, DMSO) δ : 2.30 (s, 3H, -CH$_3$) 9.4 (s, 1H,-NH), 7.23 (s, 2H,-NH$_2$), 6.7-7.7 (m,4H, Ar- H), 5.36 (s, 1H, =C-H)ppm, Mass:m/z=323 (M+1).

3-Amino-6-methyl-4,8-dioxo-2-(2'-benzothiazolyl)pyrazolo[5,4-*d*]pyrimido[1,2-*a*]-*9H*-Pyrimidine(4e): IR: 3174 cm^{-1}, 3321 cm^{-1} (-NH,-NH$_2$ strech), 1601 cm^{-1}(-C=O), ^{1}H NMR : (500 MHz, DMSO) δ : 2.3 (s, 3H, -CH$_3$) 9.4 (s, 1H,-NH), 7.2 (s, 2H,-NH$_2$), 7-8.0(m, 4H, Ar- H), 5.4 (s, 1H, =C-H)ppm; Mass:m/z=366 (M+1).

Table: 1 Physico-chemical data & Anti-oxidant evaluation using % of DPPH model.

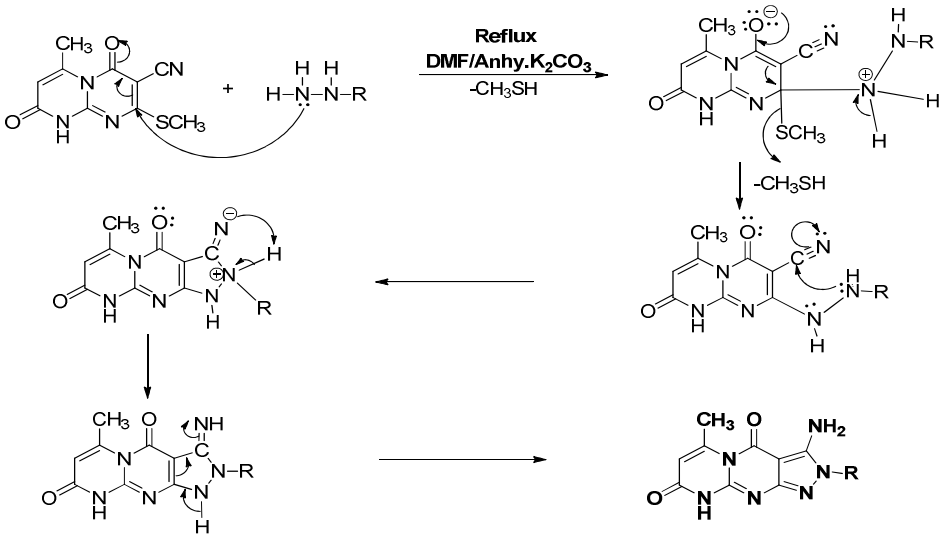
Sr.No.	Comp. code	Color	M.F.	M.Wt.	M.P.(^{0}C)	Yield (%)	DPPH (%)
1.	4a	Brown	$C_9H_8N_6O_2$	232	138 - 139	78	15.52
2.	4b	Brown	$C_{16}H_{14}N_6O_2$	322	147-150	74	15.24
3.	4c	Brown	$C_{15}H_{11}N_7O_4$	353	159-161	77	15.04
4.	4d	Yellow	$C_{15}H_{10}N_8O_6$	398	177-179	75	14.79
5.	4e	Brown	$C_{16}H_{11}N_7O_2S$	365	237-240	71	14.52
6.	4f	Brown	$C_{17}H_{13}N_7O_2S$	379	239-241	80	16.62
7.	4g	Brown	$C_{17}H_{13}N_7O_3S$	395	255-258	67	13.31
8.	4h	Yellow	$C_{16}H_{10}N_8O_4S$	410	270-272	71	13.86
Ascorbic acid as a standard							**78.48**

ANTI-OXIDANT ACTIVITY:

The proton radical scavenging action is known as an important mechanism of antioxidants. The DPPH radical scavenging assay has been used for preliminary screening of the samples for antioxidant activity.

The overall DPPH radical scavenging activity of tested 3-amino-6-methyl-4,8-dioxo-2-N (substituted) pyrazolo[5,4-*d*]pyrimido[1,2-*a*]-*9H*-Pyrimidines (4a-h) were in the range of 13.31 to 16.62 % as compared to the standard ascorbic acid 78.48 % as given in above table1. The novel synthesized compounds **4a,4b,4c,4d,4e,4f,4g & 4h** shows average DPPH radical scavenging activity as compared with ascorbic acid **(78.48%)**. It is important to note that highest DPPH radical scavenging activity was exhibited by compound **4f** is **16.62**.

Plausible mechanism of scheme II:



CONCLUSION:

In the present work we have synthesized different 3-amino-6-methyl-4,8-dioxo-2-(substituted)pyrazolo[5,4-*d*]pyrimido[1,2-*a*]-9*H*-Pyrimidine(4a-h) in good yields. Selected newly synthesized derivatives were evaluated for their free radical scavenging activities using DPPH. It is important to note that the series of novel pyrazolo-pyrimido-pyrimidines were comparatively moderate in stabilizing the DPPH free radical as compared with the standard ascorbic acid.

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