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SYNTHESIS OF (5Z)-5-SUBSTITUTED-3-[(4-HYDROXYPYRIMIDIN-2-YL)AMINO]-2-METHYL-3,5-DIHYDRO-4H-IMIDAZOL-4-ONE AND THEIR BIOLOGICAL EVALUATION

M.B. Siddesh[a], Basavaraj Padmashali[*b], K.S.Thriveni[c] and R.J. Shruthi[c]

[a]Department of Chemistry, KLE College of Engineering and Technology, Chikodi, Belagavi, Karnataka, India. E-mail: siddu.matadh@gmail.com Tel: +91 7204884480
[b]Department of Chemistry, School of Basic Sciences, Rani Channamma University, Belagavi-591156, India.
E-mail: basavarajpadmashali@yahoo.com Tel.: +91 9844218894
[c]Department of Chemistry, Sahyadri Science College, Shimoga, Karnataka, India
E-mail:thriveniks1@gmail.com; shruthirj30@gmail.com

ABSTRACT:
The compound (4Z)-4-substituted-2-methyl-1,3-oxazol-5(4*H*)-one **1a-e** prepared by the reaction of acetyl glycine, aromatic aldehydes and acetic anhydride. Further these were refluxed with 2-hydrazinyl-1,4-dihydropyrimidin-4-ol **2** in presence of pyridine to afford (5*Z*)-5-substituted-3-[(4-hydroxypyrimidin-2-yl)amino]-2-methyl-3,5-dihydro-4*H*-imidazol-4-one **3a-e.** The synthesised compounds were characterised by elemental analysis and spectral studies. The selected derivatives were studied for their antioxidant and antibactreial activities.

KEYWORDS: Oxazolones, Imidazole, antioxidant activity, antibacterial activity.

INTRODUCTION:

Imidazolinones exhibit diverse biological properties[I]. Imidazolinones have been reported to possess antifungal[II], anti-inflammatory[III], antiviral[IV], antitubercular[V], antihistamine activity[VI]. 1,2,4-trisubstituted-5-imidazolones have been reported to possess monoamine oxidase (MAO)inhibitory and anticonvulsant activity. Benzylidene derivatives are also found to posses MAO inhibitory activity [VII-VIII].
Anjani Solankee[IX] et al, have reported the synthesis and anti-microbial activity of substituted activity of imidazolinones. Hitesh D[X] et al., have reported the synthesis and antimicrobial activity of Imidazolo-quinazoline derivatives. 2-(imidazol-1-yl)pyrimidines[XI] compounds were found to inhibit the dimerization of iNOS monomers, thus preventing the formation of the dimeric, active form of the enzyme. By the screening of a combinatorial library for inhibitors of nitric oxide (NO) formation by the inducible isoform of nitric oxide synthase (iNOS) using a whole-cell assay.

The C-5 position of pyrimidine nucleus is an excellent target for modification or substitution[XII]. However, the structure activity relationship studies revealed that, C-6 position is also an important determinant for the activity.

All these stimulated our interest to synthesize some novel pyrimidines substituted imidazole derivatives of biological importance.

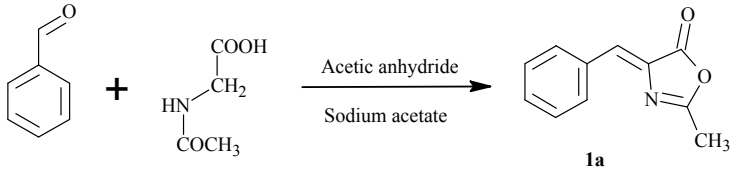
EXPERIMENTAL

MATERIALS AND METHODS:

IR spectra were recorded on Bruker alpha FT IR spectrophotometer using KBr pellets. ^{1}H NMR spectra were recorded on Bruker AV 400 MH_Z spectrometer using DMSO as solvent. Chemical shifts are expressed in δ ppm and were referenced with TMS. Mass spectra were performed on a Joel JMS-D 300 mass spectrometer operating at 70 eV. Elemental analyses were recorded using Perkin Elmer CHNS analyzer. The reactions were monitored and checked by TLC. The melting points were determined in an open capillary and were uncorrected.

Preparation of (4*Z*)-4-benzylidene-2-methyl-1,3-oxazol-5(4*H*)-one 1a

A mixture of benzaldehyde (1.20g, 0.01mole) and acetyl glycine (1.17g, 0.01mole) was taken as starting material, condensed with in presence of acetic anhydride and sodium acetate was taken in conical flask heated on electric hot plate with constant stirring. As soon as mixture liquefied completely, flask is heated on water bath. Then added ethanol slowly to the contents of the flask and allowed the mixture to stand overnight. Then filtered washed with cold ethanol and hot water, the product was recrystallized from benzene. Similarly, **1b-e** were prepared.

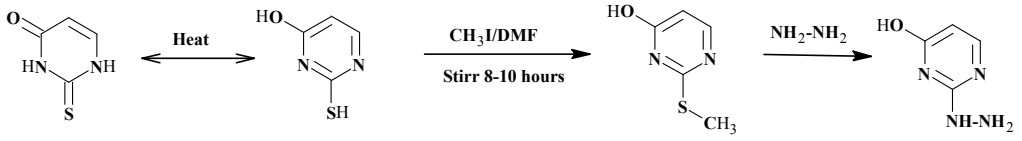


1a

Preparation of 2-hydrazinyl-1,4-dihydropyrimidin-4-ol 2:

To a solution of 2-thioxo-2,3-dihydropyrimidin-4(1*H*)-one (1.281g,0.01mole) in DMF (20 ml), potassium carbonate (1.40g,0.01ml) and methyl iodide (0.0456g,0.02 mole) were added and the mixture was refluxed with stirring for 3 hours. The completion of reaction was monitored by TLC. After the completion of the reaction, the reaction mixture was diluted with cold water and neutralised using dilute glacial acetic acid. The product separated was filtered, dried and recrystallized from ethanol.

A mixture of 2-(methylsulfonyl)-1,4-dihydropyrimidin-4-ol (2.34g,0.01mole) and hydrazine hydrate (0.32g,0.01mole) in ethanol was refluxed on a water bath for 08 hours. From the reaction mixture excess of ethanol was removed by distillation. On cooling, the solid separated was dried and recrystallized from ethanol.

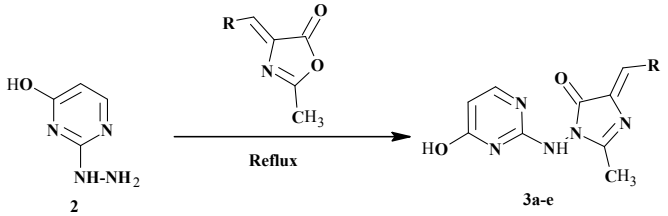


2

Preparation of (5*Z*)-5-benzylidene-3-[(4-hydroxypyrimidin-2-yl)amino]-2-methyl-3,5-dihydro-4*H*-imidazol-4-one 3a:

(4*Z*)-4-benzylidene-2-methyl-1,3-oxazol-5(4*H*)-one **1a** (1.87g, 0.01mol) was mixed with 2-hydrazinyl-1,4-dihydropyrimidin-4-ol **2** (1.26g, 0.01mol) in a dry round bottom flask and refluxed for 8 hours in dry pyridine. The completion of the reaction was monitored by TLC.

The excess pyridine was removed by distillation under reduced pressure. The content was cooled to room temperature and diluted by adding little ice cold water. The separation of product was achieved by neutralization with dilute hydrochloric acid and then product was filtered, dried and recrystallised using ethanol. Similarly, **3b-e** were prepared.



2 3a-e

(5*Z*)-5-Benzylidene-3-[(4-hydroxypyrimidin-2-yl)amino]-2-methyl-3,5-dihydro-4*H*-imidazol-4-one 3a:

3a: Solid; (71%); IR (KBr) (ν_{max} cm^{-1}): 1617 (C=N), 1699 (C=O); ^{1}H NMR (400 MH_Z, DMSO-d_6) δ (ppm): 5.41 (s, 1H, -C=CH), 4.84 (s, 1H, OH), 7.18-8.08 (m, 7H, Ar H), 1.69 (s, 3H, CH_3), 4.46 (s, 1H, NH); Elemental analysis: Calculated (%) for $C_{15}H_{13}N_5O_2$: C, 61.01; H, 4.40; N, 23.72; Found: C, 60.97; H, 4.36; N, 23.65; MS m/z: 295.

(5*E*)-5-(4-Chlorobenzylidene)-3-[(4-hydroxypyrimidin-2-yl)amino]-2-methyl-3,5-dihydro-4*H*-imidazol-4-one 3b:

3b: Solid; (66%); IR (KBr) (ν_{max} cm^{-1}): 1620 (C=N), 1692 (C=O); ^{1}H NMR (400 MH_Z, DMSO-d_6) δ (ppm): 5.57 (s, 1H, -C=CH), 4.90 (s, 1H, OH), 7.22-8.01 (m, 6H, Ar H), 1.65 (s, 3H, CH_3), 4.40 (s, 1H, NH); Elemental analysis: Calculated (%) for $C_{15}H_{12}ClN_5O_2$: C, 54.54; H, 3.63; N, 21.21; Found: C, 54.46; H, 3.57; N, 21.17; MS m/z: 330.

(5*Z*)-5-[(2-Chloroquinolin-3-yl)methylidene]-3-[(4-hydroxypyrimidin-2-yl)amino]-2-methyl-3,5-dihydro-4*H*-imidazol-4-one 3c:

3c: Solid; (64%); IR (KBr) (ν_{max} cm^{-1}): 1622 (C=N), 1676 (C=O); ^{1}H NMR (400 MH_Z, DMSO-d_6) δ (ppm): 5.60 (s, 1H, -C=CH), 4.88 (s, 1H, OH), 7.20-8.28 (m, 7H, Ar H), 1.61 (s, 3H, CH_3), 4.70 (s, 1H, NH); Elemental analysis: Calculated (%) for $C_{18}H_{13}ClN_6O_2$: C, 56.69; H, 3.41; N, 22.04; Found: C, 56.63; H, 3.39; N, 22.94; MS m/z: 381.

(5*E*)-3-[(4-Hydroxypyrimidin-2-yl)amino]-5-(4-methoxybenzylidene)-2-methyl-3,5-dihydro-4*H*-imidazol-4-one 3d:

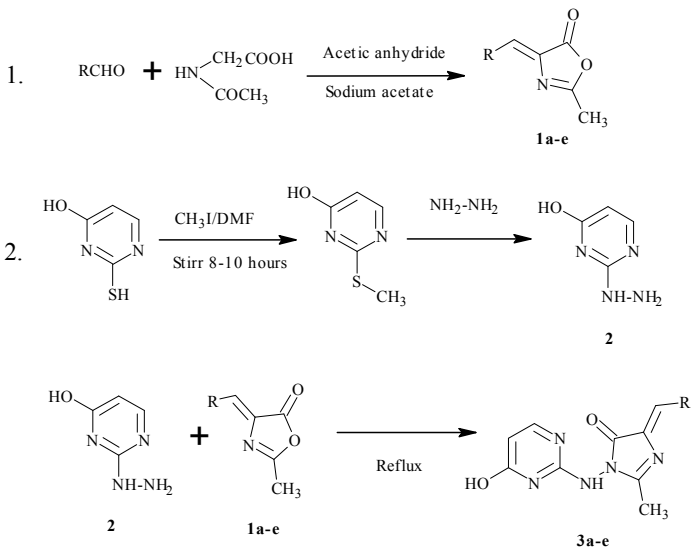
3d: Solid; (68%); IR (KBr) (ν_{max} cm^{-1}): 1630 (C=N), 1685 (C=O); ^{1}H NMR (400 MH_Z, DMSO-d_6) δ (ppm): 5.40 (s, 1H, -C=CH), 4.88 (s, 1H, OH), 7.39-8.48 (m, 6H, Ar H), 1.59 (s, 3H, CH_3), 4.50 (s, 1H, NH); Elemental analysis: Calculated (%) for $C_{16}H_{15}N_5O_3$: C, 59.07; H, 4.61; N, 21.53; Found: C, 59.02; H, 4.58; N, 21.47; MS m/z: 325.

(5*E*)-5-(Furan-2-ylmethylidene)-3-[(4-hydroxypyrimidin-2-yl)amino]-2-methyl-3,5-dihydro-4*H*-imidazol-4-one 3e:

3e: Solid; (60%); IR (KBr) (ν_{max} cm^{-1}): 1627 (C=N), 1696 (C=O); ^{1}H NMR (400 MH_Z, DMSO-d_6) δ (ppm): 5.51 (s, 1H, -C=CH), 4.82 (s, 1H, OH), 7.20-7.79 (m, 5H, Ar H), 1.67 (s, 3H, CH_3), 4.59 (s, 1H, NH); Elemental analysis: Calculated (%) for $C_{13}H_{11}N_5O_3$: C, 54.73; H, 3.85; N, 24.56; Found: C, 54.69; H, 3.80; N, 24.51; MS m/z: 285.

RESULTS AND DISCUSSION:

Substituted benzylidene-hydroxypyrimidin-imidazol derivatives **(3a-e)** were prepared by refluxing substituted benzylidene-2-methyl-1,3-oxazol-5(4*H*)-one (**1a-1e**) with 2-hydrazinyl-1,4-dihydropyrimidin-4-ol **2** in dry pyridine for 8hours. The completion of the reaction was monitored by TLC. The excess pyridine was removed by distillation under reduced pressure. The contents were cooled to room temperature and diluted by adding little ice cold water. The separation of product was achieved by neutralization with dilute hydrochloric acid and then product was filtered, dried and recrystallised using ethanol.



Scheme 1: Synthesis of (5Z)-5-substituted-3-[(4-hydroxypyrimidin-2-yl) amino]-2 -methyl-3,5-dihydro-4H-imidazol-4-one

Comp	R
3a	C_6H_5
3b	4-Cl-C_6H_4
3c	2-Chloro-quinoline-3-aldehyde
3d	C_6H_4-4-OCH_3
3e	C_4H_3O

The IR spectra of the compound (5*Z*)-5-benzylidene-3-[(4-hydroxypyrimidin-2-yl)amino]-2-methyl-3,5-dihydro-4*H*-imidazol-4-one **3a** exhibited an absorption band at 1699 cm^{-1} which is characteristics of carbonyl, another band at 1617 cm^{-1} due to C=N. ^1H NMR spectra of compound **3a** exhibited three singlets at δ 1.69, 4.46 and 5.41 respectively for the protons of CH_3, NH and –CH=C. The Mass spectrum of the compound 3a was showed molecular ion peak at m/z 295 which is in agreement with the compound.

Some of the selected compounds were studied for antibacterial and antioxidant activities. Few of the compounds found show some potent activity.

Table-1: Characterization data of synthesized compounds

Compound	Yield %	M.P. ^0C	Mol. formula (Mol.Wt)	Found % (Cacld.)		
				C	H	N
3a	71	178-182	$C_{15}H_{13}N_5O_2$ (295)	60.97 (61.01)	4.36 (4.40)	23.65 (23.72)
3b	66	168-172	$C_{15}H_{12}ClN_5O_2$ (330)	54.46 (54.54)	3.57 (3.63)	21.17 (21.21)
3c	64	187-191	$C_{18}H_{13}ClN_6O_2$ (381)	56.63 (56.69)	3.39 (3.41)	21.94 (22.04)
3d	68	175-179	$C_{16}H_{15}N_5O_3$ (325)	59.02 (59.07)	4.58 (4.61)	21.47 (21.53)
3e	60	166-170	$C_{13}H_{11}N_5O_3$ (285)	54.69 (54.73)	3.80 (3.85)	24.51 (24.56)

BIOLOGICAL ACTIVITIES

ANTIBACTERIAL ACTIVITY:

Some of the selected compounds were screened for their antibacterial activity[XIII] against *Staphylococcus aureus*, *Escherichia coli*, *S.Paratyphi A* and *Bacillus subtilis*. The activity was carried out using cupplate agar method. The zone of inhibition was measured in millimeters. DMF was used as a vehicle. Chloramphenicol was used as standard drug for comparison. The compounds were tested at 40 µg/mL concentration. Some of the compounds were found to show potent activity against bacteria. The zone of inhibition is presented in table 2.

Table-2: Antibacterial activity of the synthesized compounds

Compound	Diameter of zone of inhibition (mm)			
	Staphylococcus aureus	***Escherichia coli***	***S. Paratyphi-A***	***Bacillus Subtilis***
3a	**14**	**19**	**15**	**22**
3b	11	16	14	16
3d	**14**	**17**	**14**	**19**
DMF	00	00	00	00
Chloramphenicol	24	20	20	24

ANTIOXIDANT ACTIVITY:

The antioxidant activity of some selected compounds was tested by DPPH scavenging method[XIV]. DPPH 0.002% in methanol was used as the free radical. The optical density was measured at 517 nm using UV-Visible spectrophotometer. The absorbance of the DPPH control was also noted. The scavenging activity of the compounds against the stable DPPH was calculated using the equation. Inhibition of free radical DPPH percent (I%) or Scavenging activity (%) = (A – B) /A X 100, where 'A' was the absorbance of DPPH solution and 'B' was the absorbance of DPPH solution with compounds. Some of the compounds exhibited potent antioxidant activity. The results are shown in table 3.

Table-3: Antioxidant activity of synthesized compounds

Compound	Scavenging activity of different concentrations (µg/mL) of compounds %				
	25	**50**	**100**	**200**	**400**
3a	59.60	63.46	66.19	69.43	75.03
3b	61.44	64.08	67.68	70.57	76.70
3d	63.68	66.78	69.11	74.30	78.11
Ascorbic acid	80.30	82.19	88.04	93.70	96.11

CONCLUSIONS:

The work was mainly focused on efficient synthesis of substituted Imidazole-pyrimidine derivatives. The reactions performed are ecofriendly and few compounds have shown potent activity when compared with the standard drugs used.

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