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Microwave assisted synthesis of some 5-substituted imidazolone analogs as a new class of non purine xanthine oxidase inhibitors.

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ABSTRACT

:

*A series of 5-substituted imidazolone **1-22** analogs were synthesized by condensation of different substituted oxazolones with various aromatic amines under solvent free conditions in a microwave reactor. All the synthesised compounds were evaluated for in vitro xanthine oxidase inhibitory activity for the first time. Xanthine oxidase is a complex molybdoflavoprotein that catalyses the hydroxylation of xanthine to uric acid. Among the synthesised compounds **7**, **11**, **13**, **15** and **19** were found to be most active inhibitors with an IC_{50} ranging from 6 to 20.28 µM. Compound **7** emerged as the most potent xanthine oxidase inhibitor (IC_{50} = 6 µM) in comparison to allopurinol (IC_{50} = 11.10 µM). The structures of all the newly synthesized compounds were elucidated by using IR, ^{1}H-NMR.*

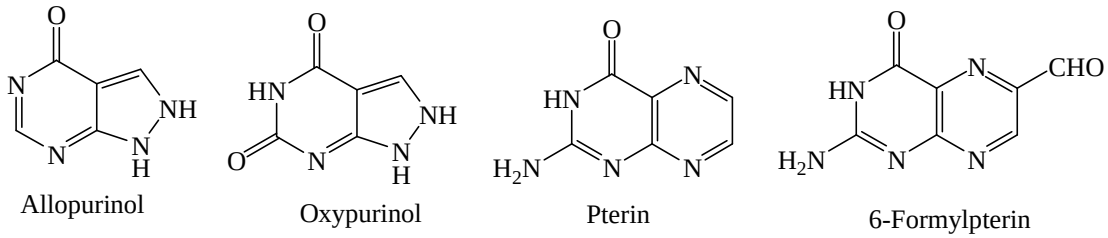
Keyword: Oxazolones, Imidazolones, xanthine oxidase, microwave.

INTRODUCTION

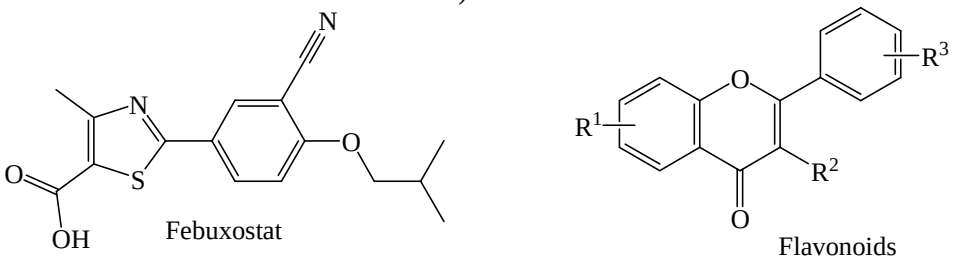
Xanthine oxidase (XO), a molybdoflavoprotein found normally in serum and the lungs, catalyses the oxidative hydroxylation of purine substrates (hypoxanthine and xanthine) to produce uric acid. The subsequent reduction of oxygen at the flavin centre generating reactive oxygen species either as superoxide anion radical or hydrogen peroxide [1-3]. Catalysis by xanthine oxidase to produce uric acid and reactive oxygen species leads to many diseases like gout and at least symptoms of diseases like oxidative damage to the tissue [2]. Generally, two types xanthine oxidase inhibitors potentially used that includes purine base compounds such as allopurinol [3-4], oxypurinol [5], 2-alkyl hypoxanthines [6], pterin, 6-formylpterin [7] etc. and non purine analogs such as feboxustat [8], flavonoids [9], 1,3-diaryltriazole derivative [10] and curcumin [11]. The structures of some reported XO inhibitors are given in **figure 1**. Since xanthine oxidase also involved in the metabolism of 6-mercaptopurine, caution should be taken before administering allopurinol and 6-mercaptopurine, or its prodrug azathioprine, in conjunction. In recent years, the researchers shows keen interest among towards structurally diverse and non-purine isosters as xanthine oxidase inhibitors because of possible interactions of purine analogs xanthine oxidase inhibitors on activities of purine and pyrimidine metabolizing enzymes leading to Steven Johnson syndrome and worsening of renal function induced in some of the patients [2-4].

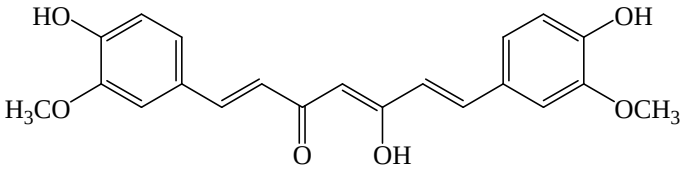
Keeping in view the shape and structural features of already reported 1-acetyl-3,5-diaryl-4,5-dihydro(1H)pyrazoles, as potent xanthine oxidase inhibitors [12], the present study investigates the potential of 5-substituted imadazolones as a new class of non purine xanthine oxidase inhibitors. Early the imidazolones have been prepared by heating a

mixture of 5-oxazolones derivatives with aromatic and substituted aromatic amine in the presence of pyridine for 10-15 hours. The yield of imidazolones was very poor and the reaction was a long time reaction [13-17]. 5-substituted imadazolones have previously been reported to exhibit a variety of biological activities including analgesic and anti-inflammatory activity [18-19], CNS depressant [20], monoamine oxidase (MAO) inhibitory [21], anticonvulsant [21-22], immnomodulator activities [23], antianthelmintic activity [24], anticancer [25], cardiovascular activity [26-27], antimicrobial [28-29] etc. In this report, we describe the synthesis of non-purine 5-substituted imidazolones **1-22** analogs under microwave irradiation as a new class of XO inhibitors for the first time. The structures of all the prepared analogs were determined by using IR, ^{1}H-NMR.



A) Purine base XO Inhibitors





B) Nonpurine base XO Inhibitors

Figure 1:structures of some reported XO inhibitors

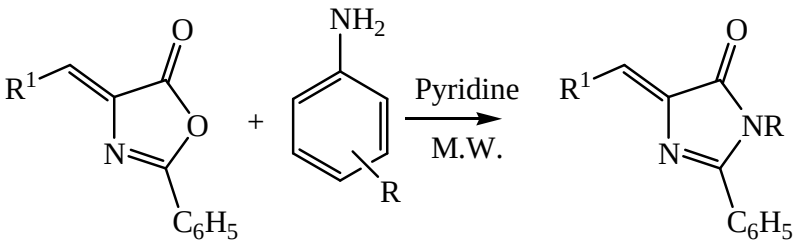
MATERIALS AND METHODS

The reagents were purchased from Sigma–aldrich, Loba and CDH, India and used without further purification. The progress of the reaction was monitored by TLC using 0.2 mm thickness aluminium sheet precoated with silica gel Merck 60F 254 and visualization was done using iodine/UV lamp for detection of the spots. The solvent was removed under reduced pressure using Buchi rotary evaporator. The prepared analogs were characterized on the basis of their spectroscopic data (IR, ^{1}H NMR). IR spectra recorded on Perkin Elmer RX1 spectrophotometer using KBr pellets and are expressed in cm^{-1}. The ^{1}H NMR spectra were recorded on Brucker 300 MHz spectrometer in ($CDCl_3$) using TMS as an internal reference and chemical shifts is measured in δ ppm. Melting points were determined by open capillary tube method and are uncorrected.

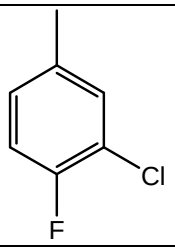
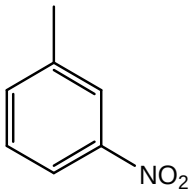
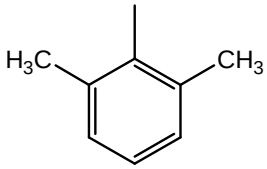
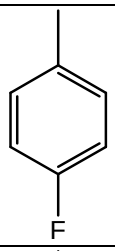
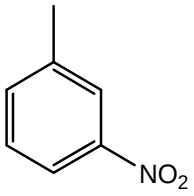
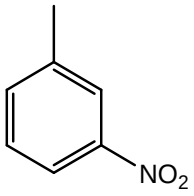
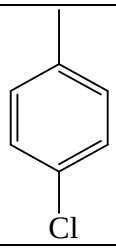
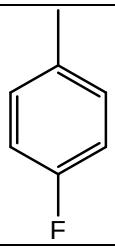
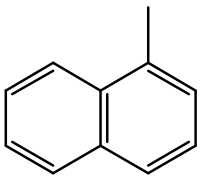
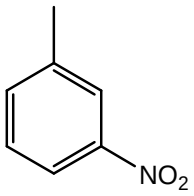
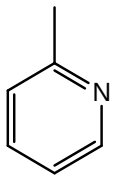
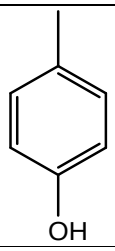
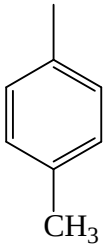
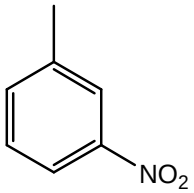
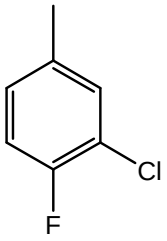
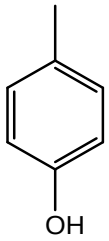
1.1. General procedure for the synthesis of title compounds (1-22)

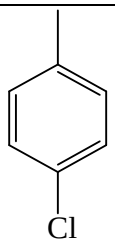
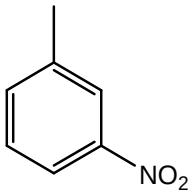
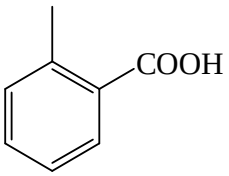
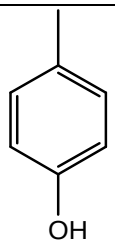
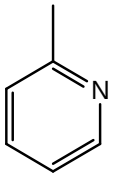
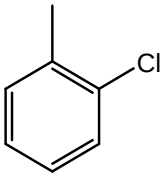
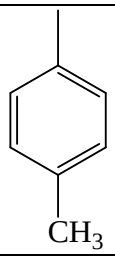
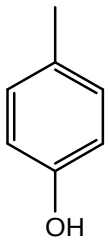
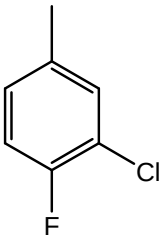
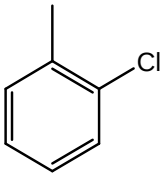
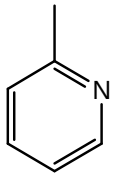
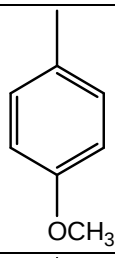
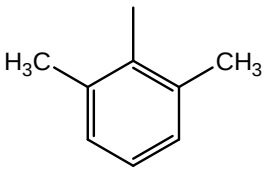
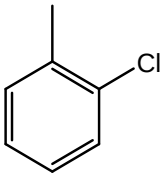
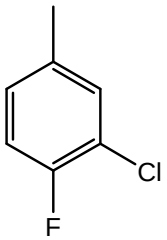
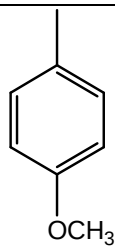
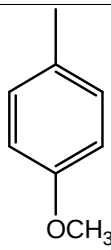
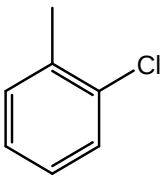
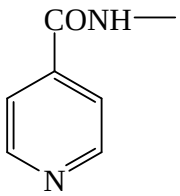
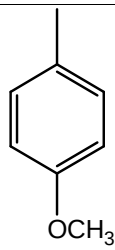
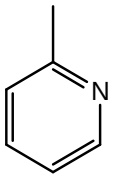
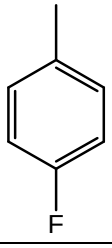
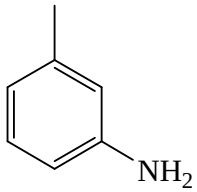
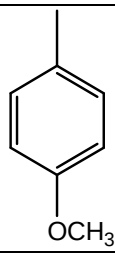
Condensation of different 5-substituted oxazolones (1 mmol) and substituted aromatic amines (1.1 mmol) in anhydrous pyridine under solvent free conditions in a microwave reactor yield 5-substituted imazolones (**1-22**) analogs (**Scheme 1**). The reaction was completed in 10-15 min. The completion of reaction was monitored by TLC

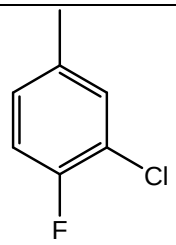
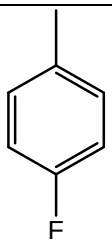
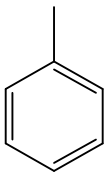
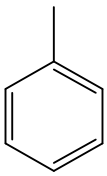
and then 5 ml of ice cool 5% HCl in water was added and the mixture was left for overnight. The resultant solids were collected and washed with water. The resultant solid was crystallized by ethanol, filtered and on drying to afford title compounds.



Scheme 1

Compound No.	R	R[1]	Compound No.	R	R[1]
1			12		
2			13		
3			14		
4			15		

5			**16**		
6			**17**		
7			**18**		
8			**19**		
9			**20**		
10			**21**		

11			**22**		

The spectral data (FTIR, ^{1}H NMR) of known compounds such as 4-(3-nitrobenzylidene)-1-(3-chloro-4-fluorophenyl)-2-phenyl-1H-imidazol-5(4H)-one (**1**), 4-(3-nitrobenzylidene)-1-(3-nitrophenyl)-2-phenyl-1H-imidazol-5(4H)-one (**2**), 4-(3-nitrobenzylidene)-1-(naphthalen-1-yl)-2-phenyl-1H-imidazol-5(4H)-one (**3**), 4-(2-chlorobenzylidene)-2-phenyl-1-(pyridin-2-yl)-1H-imidazol-5(4H)-one (**6**), 4-(2-chlorobenzylidene)-1-(3-chloro-4-fluorophenyl)-2-phenyl-1H-imidazol-5(4H)-one (**7**), 4-(4-fluorobenzylidene)-2-phenyl-1-(pyridin-2-yl)-1H-imidazol-5(4H)-one (**10**), 4-(4-fluorobenzylidene)-1-(3-chloro-4-fluorophenyl)-2-phenyl-1H-imidazol-5(4H)-one (**11**), 4-(4-fluorobenzylidene)-1-(2,6-dimethylphenyl)-2-phenyl-1H-imidazol-5(4H)-one (**12**), 4-(4-hydroxybenzylidene)-2-phenyl-1-(pyridin-2-yl)-1H-imidazol-5(4H)-one (**14**), 4-(4-hydroxybenzylidene)-1-(3-chloro-4-fluorophenyl)-2-phenyl-1H-imidazol-5(4H)-one (**15**), 4-(4-methoxybenzylidene)-2-phenyl-1-(pyridin-2-yl)-1H-imidazol-5(4H)-one (**18**), 4-(4-methoxybenzylidene)-1-(3-chloro-4-fluorophenyl)-2-phenyl-1H-imidazol-5(4H)-one (**19**) were found to be identical with those reported in the literature [30]. The physical data of ten new compounds (**4-5, 8-9, 13, 16-17, 20-22**) are provided below.

Table 1. Melting points, yields, molecular formula, molecular weight and log P values of 5-substituted imidazolones 1-22 analogs

Compound	Melting point (°C)	Yield (%)	Molecular formula	Molecular weight	LogP
1	214-216	70	$C_{22}H_{13}ClFN_3O_3$	421.81	5.47
2	217-219	72	$C_{22}H_{14}N_4O_5$	414.38	4.63
3	223-224	67	$C_{26}H_{17}N_3O_3$	419.44	5.86
4	215-217	72	$C_{23}H_{17}N_3O_3$	383.41	4.93
5	210-212	74	$C_{22}H_{14}ClN_3O_3$	403.82	5.16
6	216-217	77	$C_{21}H_{14}ClN_3O$	359.82	4.71
7	210-212	79	$C_{22}H_{13}Cl_2FN_2O$	411.26	6.16
8	197-198	73	$C_{24}H_{19}ClN_2O$	386.88	6.41
9	194-195	75	$C_{23}H_{17}ClN_2O_2$	388.85	5.24
10	238-240	76	$C_{21}H_{14}FN_3O$	343.36	4.24
11	228-230	68	$C_{22}H_{13}ClF_2N_2O$	394.81	5.70
12	238-239	60	$C_{24}H_{19}FN_2O$	370.43	5.94
13	231-232	65	$C_{22}H_{14}ClFN_2O$	376.82	5.39
14	234-235	62	$C_{21}H_{15}N_3O_2$	341.37	3.60
15	242-243	64	$C_{22}H_{14}ClFN_2O_2$	392.82	5.05
16	222-223	70	$C_{23}H_{16}N_2O_4$	384.39	3.81
17	228-230	65	$C_{23}H_{18}N_2O_2$	354.41	4.52
18	235-237	70	$C_{22}H_{17}N_3O_2$	355.40	4.13
19	225-227	72	$C_{23}H_{16}ClFN_2O_2$	406.84	5.59
20	224-225	75	$C_{23}H_{18}N_4O_3$	398.42	2.84
21	232-233	68	$C_{23}H_{19}N_3O_2$	369.42	3.87
22	180-182	76	$C_{22}H_{16}N_2O$	324.38	4.55

Molecular properties (log P values) of 5-substituted imidazolones is calculated by http://www.molinspiration.com

1.1.1. *4-(3-nitrobenzylidene)-2-phenyl-1-p-tolyl-1H-imidazol-5(4H)-one* (**4**): IR (KBr): 1620 (C=N), 1598 (C=C), 1655 (C=O) cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.28 (s, 3H, CH_3), 7.6 (s, 1H, CH), 7.04-8.20 (m, 13H, Ar-H).

1.1.2. *4-(3-nitrobenzylidene)-1-(4-chlorophenyl)-2-phenyl-1H-imidazol-5(4H)-one* (**5**): IR (KBr): 1610 (C=N), 1594 (C=C), 1655 (C=O) cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.6 (s, 1H, CH), 7.2-8.2 (m, 13H, Ar-H).

1.1.3. *4-(2-chlorobenzylidene)-1-(2,6-dimethylphenyl)-2-phenyl-1H-imidazol-5(4H)-one* (**8**): IR (KBr): 1600 (C=N), 1580 (C=C), 1650 (C=O) cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.2 (s, 6H, -CH_3), 7.7 (s, 1H, CH), 6.8-7.8 (m, 12H, Ar-H).

1.1.4. *4-(2-chlorobenzylidene)-1-(4-methoxyphenyl)-2-phenyl-1H-imidazol-5(4H)-one* (**9**): IR (KBr): 1610 (C=N), 1596 (C=C), 1645 (C=O) cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 3.8 (s, 3H, $-OCH_3$), 7.8 (s, 1H, CH), 6.8-7.6 (m, 13H, Ar-H).

1.1.5. *4-(4-fluorobenzylidene)-1-(4-chlorophenyl)-2-phenyl-1H-imidazol-5(4H)-one* (**13**): IR (KBr): 1620 (C=N), 1595 (C=C), 1650 (C=O) cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 7.2 (s, 1H, CH), 6.8-7.7 (m, 13H, Ar-H).

1.1.6. *2-(4-(4-hydroxybenzylidene)-4,5-dihydro-5-oxo-2-phenylimidazol-1-yl)benzoic acid* (**16**): IR (KBr): 1620 (C=N), 1590 (C=C), 1650 (C=O) cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 5.1 (s, 1H, -OH), 7.1 (s, 1H, CH), 6.7-8.2 (m, 13H, Ar-H), 11.2 (s, 1H, -COOH).

1.1.7. *4-(4-hydroxybenzylidene)-2-phenyl-1-p-tolyl-1H-imidazol-5(4H)-one (**17**):* IR (KBr): 1610 (C=N), 1592 (C=C), 1655 (C=O) cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 2.4 (s, 3H, $-CH_3$), 5.1 (s, 1H, -OH), 7.2 (s, 1H, CH), 6.7-7.6 (m, 13H, Ar-H).

1.1.8. *N-(4-(4-methoxybenzylidene)-4,5-dihydro-5-oxo-2-phenylimidazol-1-yl)isonicotin- amide* (**20**): IR (KBr): 3105 (Ar C-H), 1620 (C=N), 1594 (C=C), 1645 (C=O) cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 3.7 (s, 3H, $-OCH_3$), 7.5 (s, 1H, CH), 6.7-7.8 (m, 11H, Ar-H), 8.2 (s, 1H, -NH), 9.0 (d, 2H, Ar-H).

1.1.9. *4-(4-methoxybenzylidene)-1-(3-aminophenyl)-2-phenyl-1H-imidazol-5(4H)-one* (**21**): IR (KBr): 3100 (Ar C-H), 1615 (C=N), 1590 (C=C), 1660 (C=O) cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 3.5 (s, 3H, $-OCH_3$), 4.0 (s, 2H, $-NH_2$), 7.4 (s, 1H, CH), 6.6-7.8 (m, 13H, Ar-H).

1.1.10. *2,3-Diphenyl-5-[(E)-phenylmethylidene]-3,5-dihydro-4H-imidazole-4-one* (**22**): IR (KBr): 1620 (C=N), 1595 (C=C), 1650 (C=O) cm^{-1}. ^1HNMR (300 MHz, $CDCl_3$) δ: 7.7 (s, 1H, CH), 6.90-7.60 (m, 15H, Ar-H).

2.2. Biology

2.2.1. *In vitro* Xanthine oxidase inhibitory activity:

Bovine milk xanthine oxidase (grade 1, ammonium sulfate suspension, Sigma–Aldrich) activity was assayed spectrophotometrically by measuring the uric acid formation at 293 nm [31] using a Hitachi U-3010 UV–visible spectrophotometer at 25 °C. The reaction mixture contained 50 mM potassium phosphate buffer (pH 7.6), 75 µM xanthine and 0.08 units of xanthine oxidase. Inhibition of xanthine oxidase activity by various inhibitors was measured by following the decrease in the uric acid formation at 293 nM at 25 °C. The enzyme was preincubated for 5 min, with test compound, dissolved in DMSO (1% v/v), and the reaction was started by the addition of xanthine. Final concentration of DMSO (1% v/v) did not interfere with the enzyme activity. The assay of potent compounds was performed in triplicate and values were expressed as means of three experiments.

RESULT AND DISCUSSION

1.2. Synthesis of 5-substituted imidazolones

The synthesis pathway leading to the title compounds is given in **Scheme 1**. Condensation of a series of 5-substituted oxazolones with various substituted aromatic amines in the presence of anhydrous pyridine under microwave irradiation afforded the target 5-substituted imidazolones (**1-22**) analogs. The purity and structures of all the synthesized compounds have been elucidated on the basis of their spectral data including IR, ^1H NMR and mass spectra.

1.3. Biological evaluation

In vitro screening of the 5-substituted imidazolnes (**1-22**) using bovine milk xanthine oxidase (grade 1, ammonium sulfate suspension) enzymatic assay was performed as described in the literature [18]. The molecules exhibiting % inhibition of more than 60% at 50 µM were further tested in triplicate for the xanthine oxidase inhibitory activity to calculate the IC_{50} values. The XO inhibitory data of synthesized analogs was given in **Table 2**.

Table 2. *In vitro* screening of the synthesized compounds for XO inhibitory activity

Compound	Percentage inhibition (%) at 50 µM
1	**65.34**
2	**17.50**
3	**22.93**
4	**56.51**
5	**48.16**
6	**11.33**
7	**95.14**
8	**10.30**
9	**68.73**
10	**62.99**
11	**92.50**
12	**61.41**
13	**78.15**
14	**32.05**
15	**72.40**
16	**58.77**
17	**65.17**
18	**62.50**
19	**93.58**
20	**64.71**
21`	**35.05**
22	**10.03**

Table 2 clearly indicated that the 5-substituted imdazolones displayed percentage inhibition of more than 65% at 50 µM was further considered for the calculation of IC_{50} values. Among them compounds **7, 11** and **19** were the most active ones with percentage inhibition ranging from 90-95%.

Table 3. IC_{50} values of the most potent compounds

Compounds	XO inhibitory activity (IC_{50}[a] in µM)
1	**28.48**
7	**6**
9	**32.30**
11	**12.42**
13	**20.28**
15	**17**
17	**25.98**
19	**12**
Allopurinol	**11.10**

[a] *Values are means of the three experiment.*

CONCLUSION

In summary, the present investigation describes synthesis of 5-substituted imidazolones **1-22** analogs as potential xanthine oxidase inhibitors which are characterized by suitable methods such as spectroscopic evaluation like IR and ^{1}H NMR. All spectral data were in accordance with assumed structures. Among prepared analogs compound **7** was found to be most potent xanthine oxidase inhibitor (IC_{50} = 6 µM) in comparison to standard drug allopurinol (IC_{50} = 11.10 µM). The promising activity of these compounds along with the other data obtained during the study can also be useful for establishing the structure activity relationship studies and for the development of newer and potent 5-substituted imidazolone compounds as xanthine oxidase inhibitors.

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