Simple and Green way to Synthesis 5-aryl-1,2,4-Triazolidine-3-ones in Aqueous Medium

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ABSTRACT

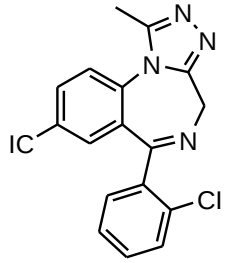
R.Ramesh and co-workers synthesized 5-aryl-1,2,4-triazolidine-3-thiones using various aromatic aldehydes, malononitrile and thiosemicarbazide by implementiry green protocol .In present work we synthesised 5-aryl-1,2,4-triazolidine-3-ones using various aromatic aldehydes, malononitrile and semicarbazide by green protocol. The new derivatives were checked good antimicrobial activities against S. aureus, E. coli and C. albicans, and A. Niger microbes.

KEYWORDS: 1,2,4-Triazolidine-3-ones,one pot synthesis, 3-component reaction, green Protocol.

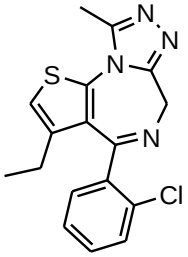
INTRODUCTION

The advancement and greening of artificial routes for the convenient access of functionalised heterocyclic motifs has become one among the foremost difficult gear up in scientific community because of the environmental and health issues, further as having the ability to accomplish the privileged targets in wonderful purity with high yields. [2] The major drive towards the cleaner processes is that the replacement of volatile organic solvent with the utilization of least expensive and promptly obtainable greener solvent systems that facilitate some organic transformation with non additional catalyst. Thus, they result in operational simplicity and remain as enticing approaches in organic and pharmaceutical chemistry [3] The exploration of prompt chemical reaction in green solvent system for the synthesis of medicinally desired heterocycles has received a grand written agreement of awareness with achieving the effectiveness that gives a lot of important route in clean synthesis. [4] Among the varied heterocycles ,nitrogen containing scaffolds have emerged as imperative motifs in prescription drugs thanks to their specified probable deeds on biological systems. They type very important avenues of a large number over present similarly as artificial bioactive molecules [5] development of never artificial ways to construct the carbon-nitrogen bond provides associate extreme potential for putting of Nitrogen into the carbon containing scaffolds [6]. In this context, triazole may be prominent- risen, five membered heterocyclic motif that has attracted extension attention due to its emergence as central key tool for the most part used in medicative industries for the preparation of privileged 'drug-like' candidates [7] .Some of the potent medication commercially accessible within the market possessing five membered heterocyclic rings with Nitrogen within the 1,2 and 4 [th] position are shown in Figure 1.Great attention in their synthesis conjointy stems from their potential existence within the fields like,dyes,agro chemical,photographic materials and corrosion

inhibition [8].Recently,1,2,4-triazole and its derivatives are used as ligands for mononuclear and oligonuclear metal complexes that shows glorius physical properties [9]



Triazolam
CNS depressant



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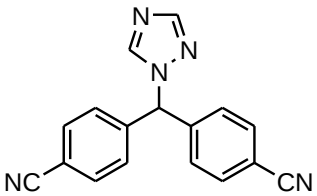
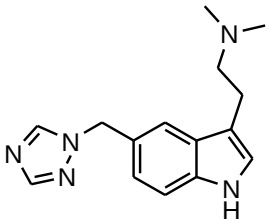
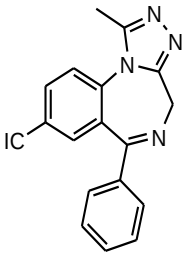
Hypnotic



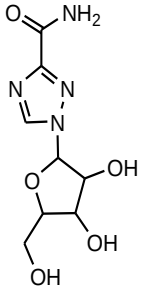
Letrozole
Breast Cancer



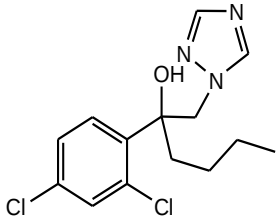
Rizatriplan
Headache



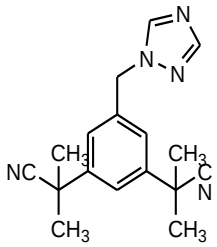
Alprazolam
Panic & anxiety disorders



Ribavarin
Anti-viral Drug



Hexaconazole
Fungicide



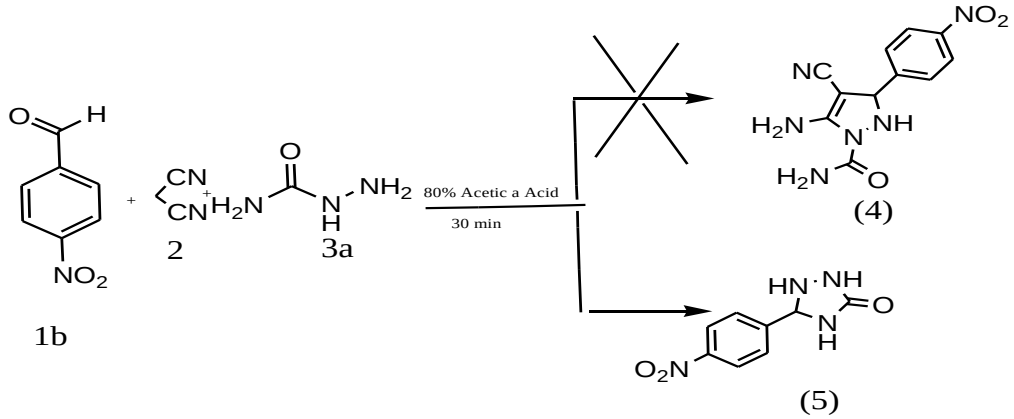
Anastrazole
Breast Cancer

To the most effective of our data, a really restricted range of report within the literature until date for the synthesis of 5-aryl-1,2,4-triazolidine-3-ones that concerned the employment of $[C_{16}MPy]$ $AICI_3Br$, [10] sulfamic acid, [11] PEG-400, [12] glycine nitrate, [13] $[2\text{-}HMPyBSA]HSO_4$ [14] and $[(Py)_2SO][HSO_4]_2$ [15] Antifungal azole like flucazole and itraconazole are robust inhibitors of lanosterol 14a-demethylase[cytochrome P45014DM] and are wide important in fungous chemotherapy.Report are offered in the development of resistance for presently offered antifungal azoles in Candida spp.,moreover as clinical failures within the treatment of fungous infections [19-22].further more, most of the current antifungal medicine don't seem to be effective against invasive Aspergillosis and also the solely drug of selection in such patients is that the injectable amphotericin B. Some example of bioactive bicyclics 1,2,4-triazole-based anxiolytic medicine are estazolam,alprazolam,5-HT1 agonist triplan drug,rizatriplan and antimicrobial medicine like spiropiperidinyl 1,2,4 triazolidine-3-one[21-27].Due to these multifarious applications, there's necessity for a green approach to synthesize bioactive spirotriazoles by victimization pronto offered beginning materials.

EXPERIMENTAL

Initially, our experimentation commenced with reaction of 4-Nitrobenzaldehyde(1b), malononitrile (2) and semicarbazide(3) as a medium in acetic acid under reflux conditions for about 1h,expected the formation of 5-amino-3-(4-Nitrophenyl)-4-cyano-2,3-dihydro-1H-pyrazole-1 carboxamide(4) because the results of a 3 component reaction. however the fashioned product was proven

to be the 5-(4-Nitrophenyl)-1,2,4-triazolidine-3-ones (5) and the yield was regarding 68% the concerns. from the structure of the product it's evident that the malononitrile has not been incorporated in its framework.



Next, the practicability of the reaction to offer product (5) was tested with group of alternative polar solvent like ethyl alcohol, methanol ,2-propanol,acetonitril as reaction media and also the yield was found to be moderate starting from 63 to 76 slightly under reflux condition. We tend to were delighted to style some economical strategy victimization green solvent system to optimise the simplest result by varied the relative concentration of water and acetic acid as binary mixture for this three component reaction.

From the result outlined in Table 1, the solvent system H_2O:CH_3COOH (1:4) at

Table 1: Effect of different solvents

Entry	Solvent	Time(min)	Yield(%)
1	CH_3CH_2OH	60	70
2	CH_3OH	60	65
3	$(CH_3)_2CHOH$	75	63
4	CH_3CN	90	50
5	**80%CH_3COOH**	**15**	**90**
6	50 % CH_3COOH	15	80

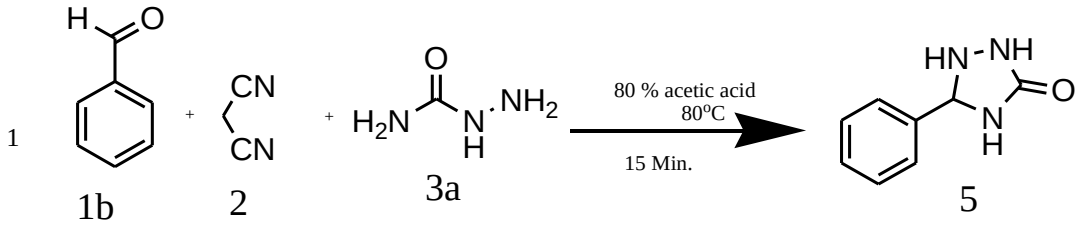
Reaction condition:4-Nitrobenzaldehyde (2 mol), malononitrile (2mol) and semicarbazide (2 mol) in solvent 10 ml under reflux conditions. Temperature was found to be highly effective for this chemistry and the corresponding target (5) was obtained in 90%.

The spectral data confirmed the formation of the unexpected compound (5) and are in fine agreement with the literature data.

Scheme 1. Cyclo condensation reaction leading to 5-(4-Nitrophenyl)-1,2,4-triazolidine -3-one in aqueous medium.

The effect of reaction temperature has conjointly been studied and once the model reaction was carried out at room temperature in the binary mixture,the yield was found to be poor even after 2h.Result from the Table. 80^o C would be the appropriate temperature, at that the reaction proceeded earlier and made

glorious result (90%) in 15 min.But ,an additional increase within the temperature didn't cause any positive result's on the product yield additionally as reaction time.



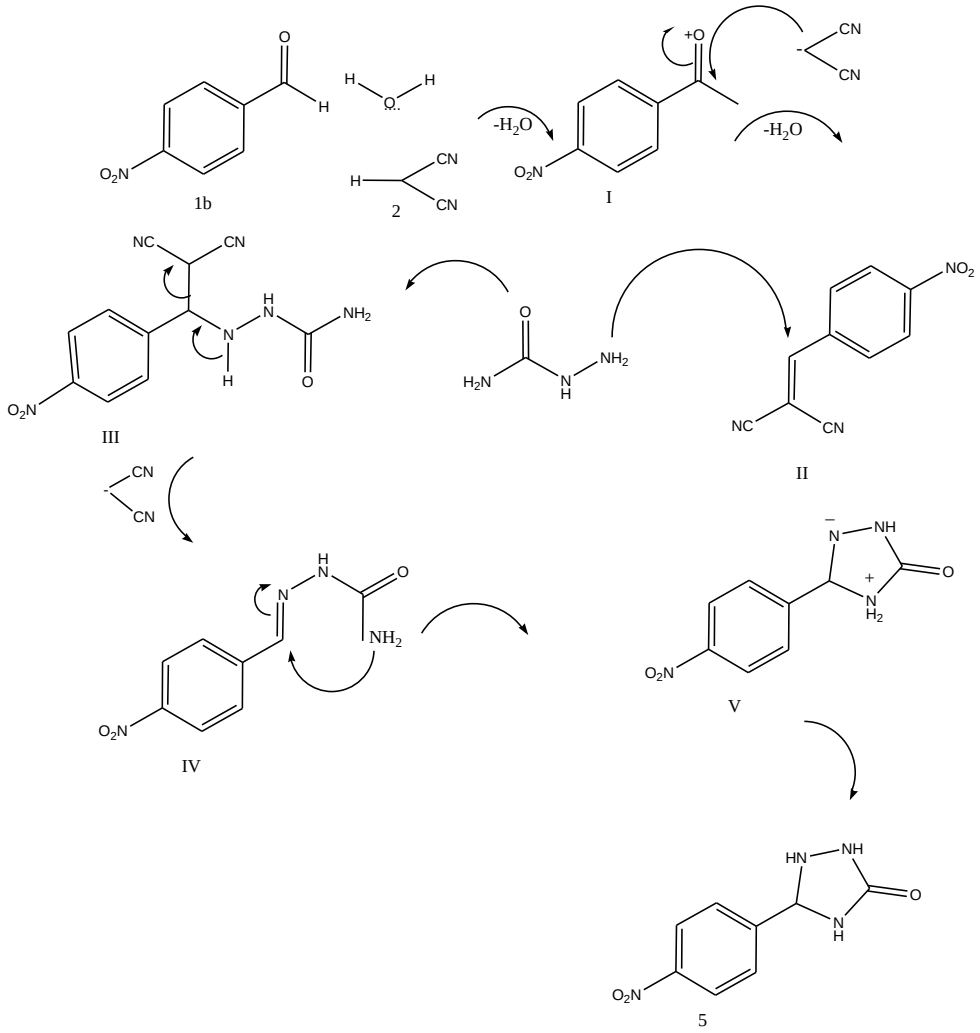
5-phenyl-1,2,4-triazolidin-3-one

Scheme 1. Cyclo condensation reaction leading to 5-(4-Nitrophenyl)-1,2,4-triazolidine-3-one in aqueous medium

Table 2.Effect of Temperature

Entry	Temperature(°C)	Time(min)	Yield (%)
1	RT	120	65
2	50	45	70
3	65	40	75
4	70	30	80
5	**80**	**15**	**90**
6	90	20	88
7	100	16	88

Reaction condition: 4-Nitrobenzaldehyde (2 mol), malononitrile (2mol) and semicarbazide (2 mol) in 80 % acetic acid (10 ml) at different temperature. isolated yields.

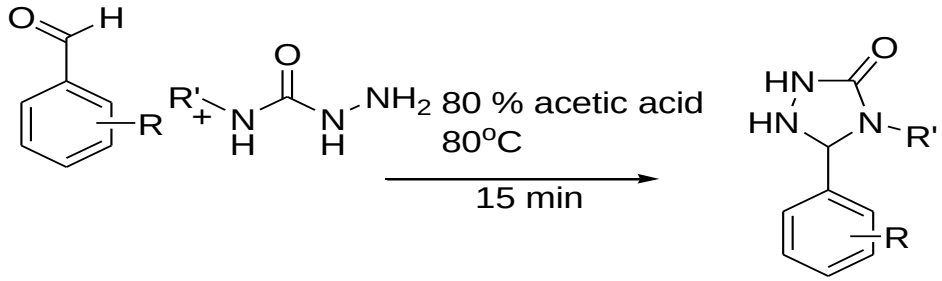


Plausible mechanism for an unexpected cyclocondensation reaction in aqueous medium

With this, a tentative mechanism that account for the synthesis of 5-aryl-1,2,4-triazolidine-3-ones via an unexpected three component reaction has been proposed in Scheme 2.here in we hypothesised that the substrate could be activated by water, as a result of it's high static permittivity (eV=78.4)[16] whereas a trifle quantity of acetic acid is needed for the dissolution of the reagents. In line with this proposal, hydrogen bonding between the hydrogen of water molecule and carbonyl oxygen atom of organic compound (1b) raised the electrophilicity of carbonyl carbon. Meanwhile ,the formation of hydrogen bond between the oxygen atom of water with acidic hydrogen of malononitrile(2)might have enhanced the nucleophilicity of compound (2). coincidental activation may need been achieved by water as good medium [17] The generated nucleophile undergoes intermolecular nucleophilic attack at the carbonyl carbon of organic compound(1)that provides the knoevenagel adduct(II) by the removal of water molecule. Then the semicarbazide (3a) added to the reaction mixture resulting in the nucleophilic addition with the arylidenemalononitrile(II) to furnish the intermediate III.In this step,malononitrile acts as an excellent leaving group[18]because of the greater electron affinity of –CN moiety resulting in the

formation of oxosemicarbazone (IV).Finally, the intermediate IV undergoes resulting interamolecular nucleophilic addition by the free NH_2 group to yield an surprising 5-(4-Nitrophenyl)-1,2,4-triazolidine-3-one (5)

On the other hand, we have examined the reaction in the absence of C-H activated acidic compound 2 i.e.1 and 3 reacted together in the optimized green solvent system at 80^o C to yield 5 (90%) as product in 10 min. with the encouraging result in hand. This two component cyclo condensation reaction has been readily diversified through the combination of a range of other substituted aromatic aldehyde 1(a-p) and semicarbazide 3(a-c).Aldehyde bearing electron withdrawing (nitro,chloro,bromo or fluoro)and electron-donating substituents (hydroxyl, methyl, or methoxy) were almost converted eventually into their corresponding targets 5(a-p).result from the Table 3.lead to conclude that, the aldehyde with substituents in the ortho position were converted into the desired product with slightly lower yield.(Table 3,Entries 10,13,14,15 and 16) which may perhaps be due to the steric hindrance of the substituents.to probe the scope and effectiveness of this methodology,it was further checked with the methyl (3b) and phenyl (3c) substituted semicarbazide which underwent the reaction successfully to afford the N-substituted 5-aryl-1,2,4-triazolidine-3-ones 5(q-v) and 5(w-y) in good yield (Table 3,Entries17-25)



Scheme 4.Synthesis of 5-aryl-1,2,4-triazolidine-3-ones

RESUlLTS AND DISCUSSION

It is value noting that, the work up of this technique involves only easy filtration leading to highly pure compounds, that were confirmed by IR, LCMS,^{1}H NMR,^{13}C NMR analyses. ^{1}H NMR spectrum of the compound 5 exhibited three notable singlet at d 10.63,6.70 ppm confirming the presence of 3 –NH proton and the singlet at d 7.93 ppm highlight the presence of benzylic methane proton, the aromatic protons on p-Nitro substituted system shows exhibited doublets at d 8.21,8.02 .IR spectrum shows dissimilar absorption bands at 3441,3178 and 3070 cm-1 respectively, which indicate the existence 3-NH stretching and conjointly a band at 1666 cm-1 representing the presence of –C=O stretching .in the 13 C NMR spectrum, a peak at d 156 ppm denotes the presence of oxy-carbonyl moiety. In addition, the LCMS showed a molecular ion peak m/z at 207.01 M^{-}

Supporting information

The general experimental section including synthetic procedure and analytical data of all 5-aryl 1,2,4-triazolidine-3-ones(IR,^{1}H NMR,^{13}C NMR,LCMS and elemental analysis) have been provided in the supporting information.

Antimicrobial activity: The antimicrobial activity of newly synthesized compounds (5)was determined against *E.coli (*Gram+ve),*S.aureus*(Gram-ve) bacteria and fungi such as *A.niger*

,*C.albicans*.The antimicrobial activity evaluation was performed using fungi reseeded in Crazek Dox agar for 48 hr at 25^{O} C and bacteria reseeded in Muller- Hinton broth for 24 hr at 37^{O}C. The standard strains required for antimicrobial assay was obtained from Microbial Culture Collection Centre, Pune, Maharashtra, India. The antimicrobial activities of tested samples were carried out in triplicate against E.coli (Gram+ve),*S.aureus* (Gram-ve) bacteria and fungi such as *A. niger, C. albicans*.

Table 1: Antimicrobial screening of compounds (5):Inhibition Zone Diameter (mm)

Compound	**µg/ml**	***E. coli***	***S. aureus***	***A.niger***	***C. albicans***
		ATCC25922	**ATCC29737**	**MCIM 545**	**MTCC 277**
(5a)	**200**	14 ± 0.8	10 ± 0.8	14 ± 0.6	15 ± 1.3
	100	12 ± 0.8	08± 0.4	12 ± 0.3	13 ± 0.7
	50	09 ± 0.3	0.7 ± 0.3	10 ± 0.7	10 ± 0.4
(5b)	**200**	15 ± 0.4	11 ± 0.7	13 ± 0.8	14 ± 1.0
	100	13 ± 0.7	0.9 ± 0.3	11 ± 0.5	11 ± 0.5
	50	11 ± 0.2	07 ± 0.5	08 ± 0.7	09 ± 0.3
(5c)	**200**	18 ± 0.8	12 ± 0.4	17 ± 0.3	16 ± 0.5
	100	16 ± 0.5	10 ± 0.4	15 ± 0.4	14 ± 0.7
	50	13 ± 0.4	08 ± 0.7	12 ± 0.3	12 ± 0.3
(5d)	**200**	19 ± 0.3	13 ± 0.3	12 ± 0.4	14 ± 0.5
	100	17 ± 0.5	11± 0.5	10 ± 0.3	12 ± 0.7
	50	14 ± 0.6	0.8 ± 0.7	08 ± 0.6	10 ± 0.4
(5e)	**200**	16 ± 0.5	12 ± 0.3	10 ± 0.3	12 ± 0.6
	100	14 ± 0.3	10 ± 0.6	0.8 ± 0.7	10 ± 0.4
	50	11 ± 0.4	07 ± 0.4	07 ± 0.5	08 ± 0.8
(5f)	**200**	13 ± 0.7	10 ± 0.5	12 ± 0.8	13 ± 0.7
	100	10 ± 0.6	07 ± 0.3	10 ± 0.4	11 ± 0.3
80	**50**	0.8 ± 0.3	_	08 ± 0.6	08 ± 0.2

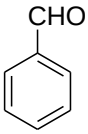
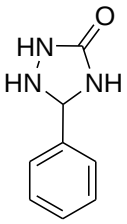
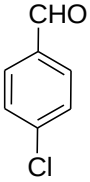
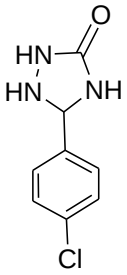
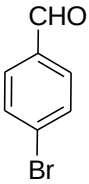
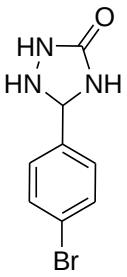
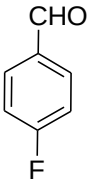
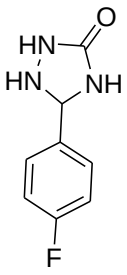
Gentamicin (10 µg/ mL) and Fluconazole (20 µg/ mL) Inhibition Zone = 9-15 mm: slight activity, 16-20 mm: moderate activity, 21 -25 mm : high activity, >26 mm: excellent activity

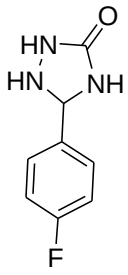
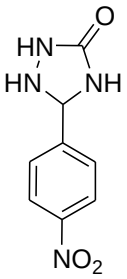
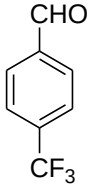
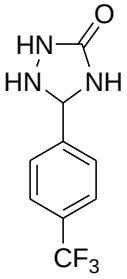
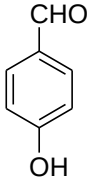
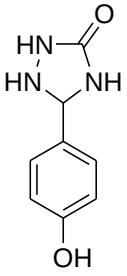
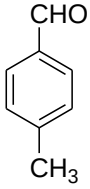
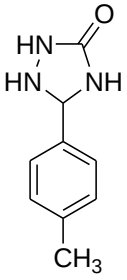
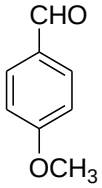
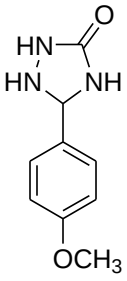
DMSO was loaded negative control.The solution of the test samples were prepared in DMSO in desired concentrations of 200,100,50 µg / mL.The Gentamicin (10 µg / mL)and Fluconazole (20 µg / mL)were used as standard for antimicrobial activity .The zone of inhibition (mm) was measured as per National Committee for Chemical laboratory Standard (NCCLS,M7-A5,January 2000).The antimicrobial activity of 3-nitroaniine was more than 4-chloroaniline and 4-bromoaniline.The compound (5)exhibited excellent antibacterial activities against Gram +ve and Gram –ve bacteria viz.*Staphylococcus aureus*, *Escherichia coli* with MIC *10 µg / ML* due to presence of p-nitro group.Also compound (5) showed excellent antifungal activities against Aspergillus niger and Candida albicans with MIC 10 µg / mL may be due to presence of nitro group.The compound 5 showed moderate antibacterial avtivity against Escherichia coli with MIC *20 µg / mL* when compared with Gentamicin. The compound (5)and showed excellent antifungal activities against *Aspergillus niger* (MCIM 545).Similarly, compounds (5) showed equivalent antifungal activitiesagainst *Candida albicns* with MIC *20 µg / mL* as compared with Fluconazole.

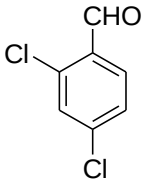
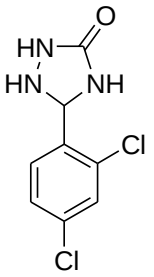
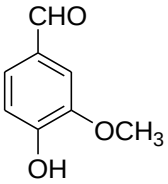
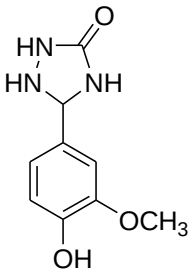
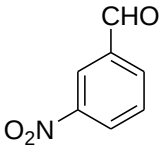
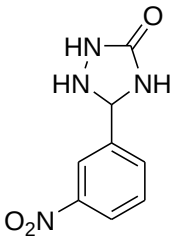
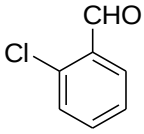
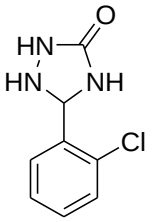
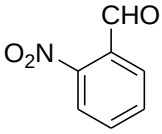
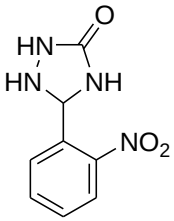
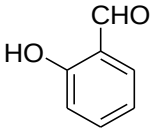
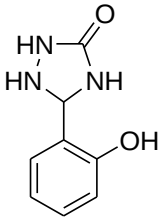
Table 2: Antimicrobial screening of compounds (5): MIC in µg / mL values

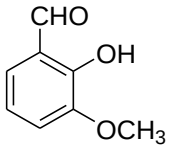
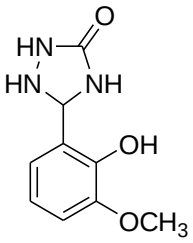
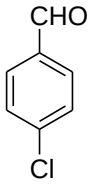
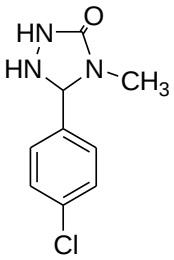
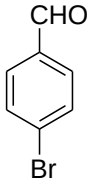
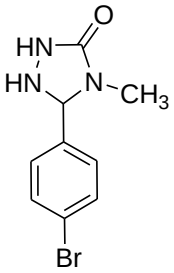
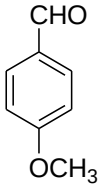
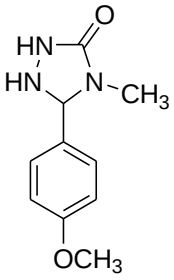
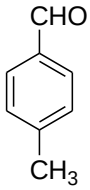
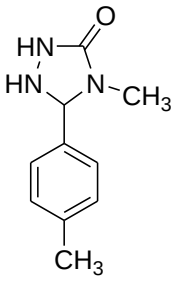
Compd	*E. coli* ATCC25922	*S. aureus* ATCC29737	*A.niger* MCIM 545	*C. albicans* MTCC 277
5a	200	400	200	200
5b	200	400	200	200
5c	200	400	100	100
5d	50	400	400	200
5e	100	400	400	400
5f	400	400	400	400

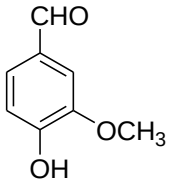
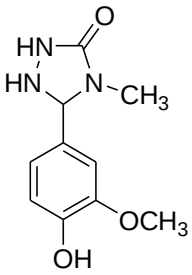
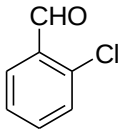
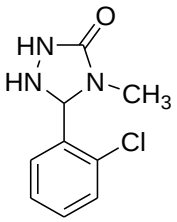
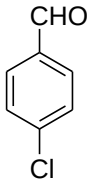
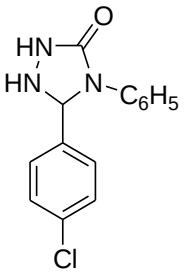
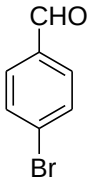
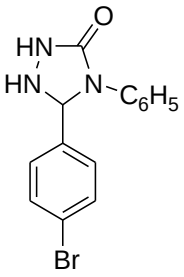
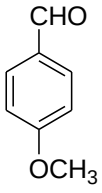
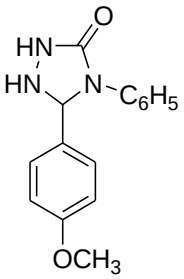
Table: 3 Synthesis of 5-aryl-1,2,4-triazolidine-3-one derivatives

Entry	Aldehyde	R'	Product	Time(min)	Yield (%)
1		H		10	90
2		H		9	92
3		H		9	91
4		H		9	89

5		H		9	91
6		H		9	90
7		H		12	90
8		H		10	90
9		H		12	89

10		H		10	85
11		H		15	91
12		H		8	95
13		H		8	90
14		H		8	88
15		H		15	85

16		H		15	86
17		CH_3		10	91
18		CH_3		10	91
19		CH_3		15	94
20		CH_3		10	95

21		CH_3		10	94
22		CH_3		12	94
23		C_6H_5		15	90
24		C_6H_5		15	90
25		C_6H_5		15	86

CONCLUSIONS

We have developed a very concise, economical and an ecofriendly technique for the synthesis of 5- aryl-1,2,4-triazolidine-3-ones by one-pot reaction of various aromatic aldehyde,Malononitrile, and semicarbazides. This protocol commence through the tandem CN bond formation and intramolecular

nucleophilic attack .This simple chemistry is in placid agreement with the neutral reaction conditions, short reaction time, wide substrate scope and smart product yields. Further investigation for the synthesis of targeted 1H-pyrazol based mostly nucleus is currently underway in our laboratory.

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