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A NEW ROUTE FOR THE SYNTHESIS OF FUNCTIONALIZED β-LACTAM ANTIBIOTIC

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ABSTRACT

We report an efficient and novel synthesis of functionalized β-lactam in three steps through Ugi-4CR in the presence of fluorite as catalyst followed by [2+2] cyclocondensation reaction. The reaction has been performed in one-pot under benign conditions. A microwave-mediated synthesis followed by conventional stirring at room temperature achieved the desired compounds 9(a-f) in good yields of about 82-89%. All the compounds 9(a-f) were screened *in vivo* anti-inflammatory and *in vitro* antibacterial activities for their potential biological efficacy. The screening data reveals that Ugi derived lactam derivatives 9a, 9c and 9e are potent anti-inflammatory agents while 9a, 9c, 9d, 9e and 9f are potential antibacterial agents. All synthesized compounds 9(a-f) were proved to be extremely active biological agent with respect to reference drugs used.

KEYWORDS: **Anti-inflammatory, Antibacterial, β-lactam, Fluorite, Staudinger reaction, U-4CR.**

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INTRODUCTION

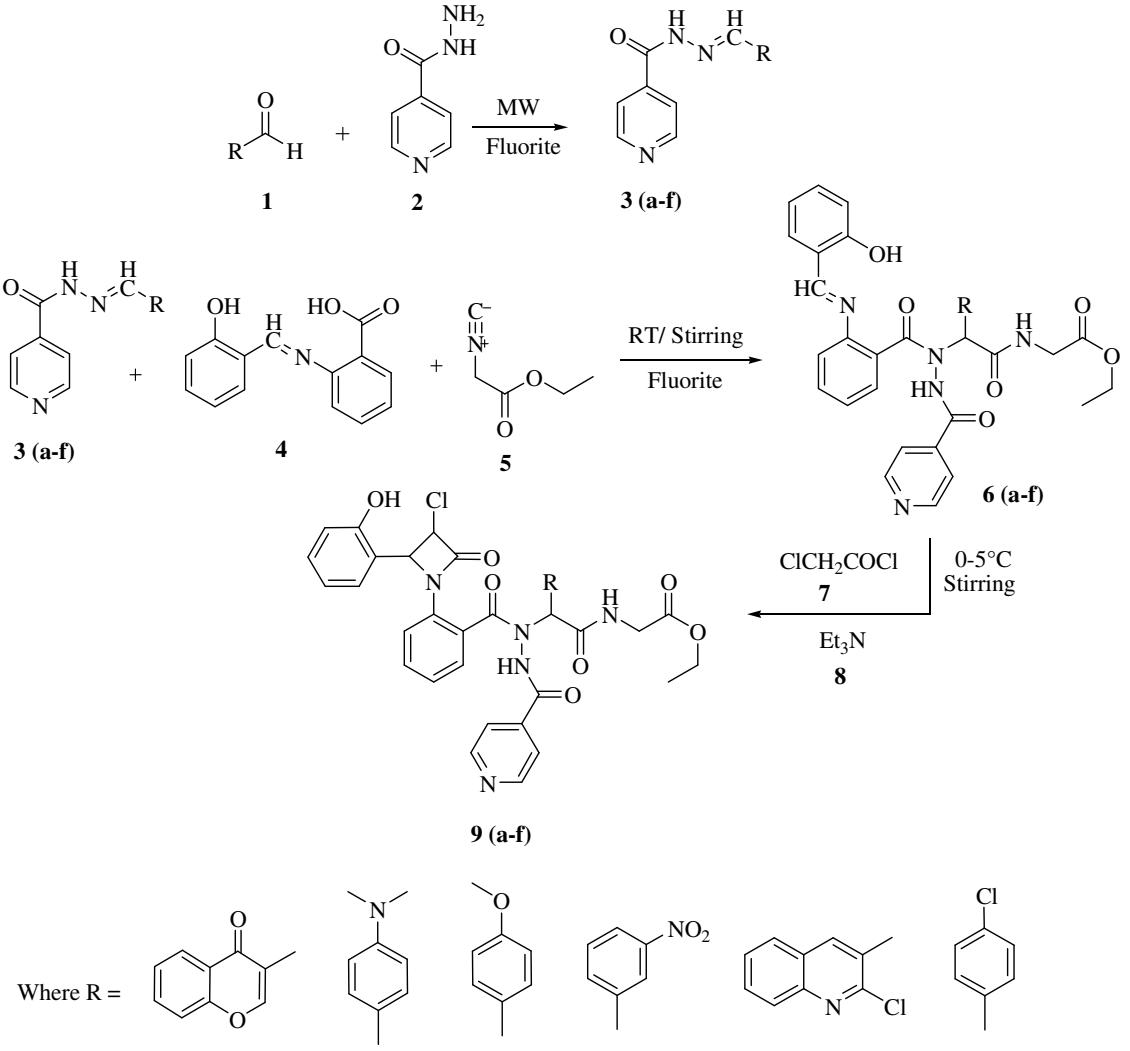
Combinatorial chemistry[1, 2] has been widely used for drug discovery process followed by identification and optimization of starting materials[3]. Several advanced methods were associated such as microwave[4-6] and ultrasound[7] techniques for the synthesis of drug moieties with speedy and high throughput synthesis. Hence, molecular diversity has been important for the development of biologically functional compounds for use in pharmaceutical chemistry[8, 9]. One of the methods for rapidly obtaining a divergent, heterocyclic molecular library[10, 11] used in organic synthesis is multicomponent reactions[12-14]. Particularly appreciated MCR, Ugi four component reaction (U-4CR)[15-17] has grown enormously and provided a profusion of novel reactions, new smart strategies as well as forward-looking methods, and high product diversity[18]. U-4CR has been reported with numerous homogenous and heterogeneous catalysts under different reaction conditions[19-21]. Schiff bases were used as substrates in the preparation of biologically active compounds which are known to possess activities such as antimicrobial[22], antifungal, anti-inflammatory and analgesics[23, 24]. Similarly, hydrazide derivatives have attracted continuing interest over the years because of their wide range of biological activities *viz.* anti-malarials[25], anti-inflammatory, analgesics[26] and antimicrobial[27] activities. Isoniazid (INH) has the greatest bactericidal activity[28] and is used in the first line treatment of tuberculosis[29]. β-lactam or 2-azetidinone structural unit containing compounds were widely known potential biological agents. It is the core structure of several antibiotic families and has similar mechanism of action against bacteria. Moreover, it was identified that the biological activity was executed by the β-lactam molecules on the type of substituent linked to the nitrogen N-1, C-3 and C-4 carbon atoms of the four-membered ring. It also depends on the stereochemistry of the β-lactam skeleton[30]. The [2+2] cycloaddition of ketenes and imine, known as Staudinger synthesis[31] was probably the most widely used method for the asymmetric synthesis of β-lactams. As an extension of our work with U-4CR[32, 33], we became interested in β-lactam synthesis by sequential Ugi reaction protocol to expand the scope of scaffold generated by the use of combinatorial synthesis of heterocyclic compounds. Hence, by using fused Schiff's base and isoniazid as a starting material in the core structure of U-4CR, we report one-pot, three steps benign synthesis of functionalized β-lactam through U-4CR using fluorite[34] as catalyst followed by Staudinger cyclocondensation reaction at room temperature under mild reaction conditions. The synthesized compounds 9(a-f) were screened for *in vivo* anti-inflammatory and *in vitro* antibacterial activities and discussed.

MATERIALS AND METHODS

Commercially available reagents and solvents were used without further purification. IR was checked on Schimadzu-IR Prestige 21 spectrometer using KBr technique (υ_{max} in cm^{-1}). ^1H NMR spectra were recorded on a Bruker-Avance II (400MHz), Varian-Gemini (100MHz) spectrophotometer using DMSO-d_6 solvent and TMS as an internal standard. Thin layer chromatography (TLC) was carried out on 5x20cm plates with a layer thickness of 0.25mm. Mass spectra were recorded on Micromass Q-T of high resolution mass spectrometer. The *in vivo* experimental protocol was approved by Institutional Animal Ethics Committee (IAEC) (Approval No. SPCP/2013/595). The experiments and care of laboratory animals was according to current ethical guidelines by the Committee for the Purpose of Control and Supervision on Experiments on Animals (CPCSEA), The Ministry of Environment and Forests (MoEF), Govt. of India, New Delhi.

Scheme 1

Synthesis of β-lactam derived from Ugi four component reaction (U-4CR)



(i) Protocol for the synthesis of compound 3(a-f)

A substituted benzaldehyde (0.01M) and isonicotinylhydrazine (0.01M) was dissolved in 95% ethanol. The reaction mixture was irradiated under MW at 120W in presence of Fluorite as a catalyst for 1-2 min (Scheme 1). After completion, the reaction mixture was poured in an ice bath. The catalyst was recovered and the crude product was purified from hot ethanol. The product was obtained in 91-97% yield. The following are the spectral data of the synthesized compounds.

N'-((4-oxo-4H-chromen-3-yl)methylene)isonicotinohydrazide (3a)

FTIR: 3215 (-NH), 3100 (-CH, Ar). ^{1}H NMR: 8.55 (1H, s, -CO-*NH*-), 8.35 (1H, s, -*CH*=N-). MS (M^+): 293.08.

N'-(4-(dimethylamino)benzylidene)isonicotinohydrazide (3b)

FTIR: 3220 (-NH), 3110 (-CH, Ar). ^{1}H NMR: 8.53 (1H, s, -CO-*NH*-), 8.31 (1H, s, -*CH*=N-). MS (M^+): 268.13.

N'-(4-methoxybenzylidene)isonicotinohydrazide (3c)

FTIR: 3225 (-NH), 3120 (-CH, Ar). ^{1}H NMR: 8.51 (1H, s, -CO-*NH*-), 8.36 (1H, s, -*CH*=N-). MS (M^+): 255.10.

N'-(3-nitrobenzylidene)isonicotinohydrazide (3d)

FTIR: 3215 (-NH), 3116 (-CH, Ar). ^{1}H NMR: 8.50 (1H, s, -CO-*NH*-), 8.22 (1H, s, -*CH*=N-). MS (M^+): 270.08.

N'-((2-chloroquinolin-3-yl)methylene)isonicotinohydrazide (3e)

FTIR: 3210 (-NH), 3110 (-CH, Ar). ^{1}H NMR: 8.52 (1H, s, -CO-*NH*-), 8.31 (1H, s, -*CH*=N-). MS (M^+): 310.06.

N'-(4-chlorobenzylidene)isonicotinohydrazide (3f)

FTIR: 3220 (-NH), 3110 (-CH, Ar). ^{1}H NMR: 8.52 (1H, s, -CO-*NH*-), 8.36 (1H, s, -*CH*=N-). MS (M^+): 259.05.

(ii) Protocol for the synthesis of Ugi product 6(a-f)

A compound 3 (0.01M), compound 4 (0.01M), ethyl isocyanoacetate 5 (0.01M) was dissolved in 5ml of 95% ethanol. The reaction mixture was magnetically stirred at room temperature in presence of Fluorite as catalyst for 4-6h (Scheme 1). After completion, the reaction mixture was poured in an ice bath. The catalyst was recovered and crude product was purified from hot ethanol. All the products were obtained in 87-93% yields. The following are the spectral data of synthesized compounds.

Ethyl2-(2-(1-(2-(2-hydroxybenzylideneamino)benzoyl)-2-isonicotinoylhydrazinyl)-2-(4-oxo-4H-chromen-3-yl)acetamido)acetate (6a)

FTIR: 3420 (-OH), 3225 (-NH), 3026 (-CH, Ar). ^{1}H NMR: 11.26 (1H, s, -OH), 8.37 (1H, s, -*CH*=N-), 8.16 (1H, s, -CO-*NH*-CH_2-), 7.10 (1H, s, -CO-*NH*-N-), 5.22 (1H, s, -CO-*CH*-C-). MS (M^+): 647.20.

Ethyl2-(2-(4-(dimethylamino)phenyl)-2-(1-(2-(2-hydroxybenzylideneamino)benzoyl)-2-isonicotinoylhydrazinyl)acetamido)acetate (6b)

FTIR: 3418 (-OH), 3226 (-NH), 3021 (-CH, Ar). ^{1}H NMR: 11.26 (1H, s, -OH), 8.35 (1H, s, -*CH*=N-), 8.13 (1H, s, -CO-*NH*-CH_2-), 7.15 (1H, s, -CO-*NH*-N-), 5.24 (1H, s, -CO-*CH*-C-). MS (M^+): 622.25.

Ethyl2-(2-(1-(2-(2-hydroxybenzylideneamino)benzoyl)-2-isonicotinoylhydrazinyl)-2-(4-methoxyphenyl)acetamido)acetate (6c)

FTIR: 3416 (-OH), 3220 (-NH), 3010 (-CH, Ar). ^{1}H NMR: 11.29 (1H, s, -OH), 8.33 (1H, s, -*CH*=N-), 8.18 (1H, s, -CO-*NH*-CH_2-), 7.18 (1H, s, -CO-*NH*-N-), 5.28 (1H, s, -CO-*CH*-C-). MS (M^+): 609.22.

Ethyl2-(2-(1-(2-(2-hydroxybenzylideneamino)benzoyl)-2-isonicotinoylhydrazinyl)-2-(3-nitrophenyl)acetamido)acetate (6d)

FTIR: 3400 (-OH), 3233 (-NH), 3015 (-CH, Ar). ^{1}H NMR: 11.25 (1H, s, -OH), 8.36 (1H, s, -*CH*=N-), 8.25 (1H, s, -CO-*NH*-CH_2-), 7.22 (1H, s, -CO-*NH*-N-), 5.32 (1H, s, -CO-*CH*-C-). MS (M^+): 624.20.

Ethyl2-(2-(2-chloroquinolin-3-yl)-2-(1-(2-(2-hydroxybenzylideneamino)benzoyl)-2-isonicotinoylhydrazinyl)acetamido)acetate (6e)

FTIR: 3421 (-OH), 3230 (-NH), 3020 (-CH, Ar). ^{1}H NMR: 11.28 (1H, s, -OH), 8.35 (1H, s, -*CH*=N-), 8.22 (1H, s, -CO-*NH*-CH_2-), 7.18 (1H, s, -CO-*NH*-N-), 5.34 (1H, s, -CO-*CH*-C-). MS (M^+): 664.18.

Ethyl2-(2-(4-chlorophenyl)-2-(1-(2-(2-hydroxybenzylideneamino)benzoyl)-2-isonicotinoylhydrazinyl)acetamido)acetate (6f)

FTIR: 3422 (-OH), 3216 (-NH), 3022 (-CH, Ar). ^{1}H NMR: 11.26 (1H, s, -OH), 8.34 (1H, s, -*CH*=N-), 8.26 (1H, s, -CO-*NH*-CH_2-), 7.16 (1H, s, -CO-*NH*-N-), 5.38 (1H, s, -CO-*CH*-C-). MS (M^+): 613.17.

(iii) Protocol for the synthesis of Ugi derived β-lactam 9(a-f)

A mixture of Ugi product 6(a-f) (0.01M) and triethylamine 7 (0.03M) in anhydrous dichloromethane (50ml), a solution of chloroacetyl chloride 8 (0.01M) was added dropwise at 0-5 °C and stirred at room temperature for 2-4h. After completion, the mixture was poured in ice bath. The crude product was purified from hot ethanol. The desired products were obtained in 82-89% yield economy. The following are the spectral data of synthesized compounds.

Ethyl2-(2-(1-(2-(3-chloro-2-(2-hydroxyphenyl)-4-oxoazetidin-1-yl)benzoyl)-2-isonicotinoylhydrazinyl)-2-(4-oxo-4H-chromen-3-yl)acetamido)acetate (9a)

FTIR: 3450 (-OH), 3310 (-NH), 3116 (-CH, Ar), 1780 (-C=O, β-lactam). ^{1}H NMR: 11.28 (1H, s, -OH), 8.52 (1H, s, -CO-*NH*-CH_2-), 8.15 (1H, s, -CO-*NH*-N-), 5.44 (1H, d, J=4.7 Hz, -C*H*), 5.23 (1H, s, -CO-*CH*-C-), 5.16 (1H, d, J=4.8 Hz, -C*H*). MS (M^+): 723.17.

Ethyl2-(2-(1-(2-(3-chloro-2-(2-hydroxyphenyl)-4-oxoazetidin-1-yl)benzoyl)-2-isonicotinoylhydrazinyl)-2-(4-(dimethylamino)phenyl)acetamido)acetate (9b)

FTIR: 3453 (-OH), 3316 (-NH), 3121 (-CH, Ar), 1782 (-C=O, β-lactam). ^{1}H NMR: 11.25 (1H, s, -OH), 8.58 (1H, s, -CO-*NH*-CH_2-), 8.17 (1H, s, -CO-*NH*-N-), 5.44 (1H, d, J=4.7 Hz, -C*H*), 5.21 (1H, s, -CO-*CH*-C-), 5.16 (1H, d, J=4.8 Hz, -C*H*). MS (M^+): 698.23.

Ethyl2-(2-(1-(2-(3-chloro-2-(2-hydroxyphenyl)-4-oxoazetidin-1-yl)benzoyl)-2-isonicotinoylhydrazinyl)-2-(4-methoxyphenyl)acetamido)acetate (9c)

FTIR: 3456 (-OH), 3320 (-NH), 3110 (-CH, Ar), 1780 (-C=O, β-lactam). ^{1}H NMR: 11.28 (1H, s, -OH), 8.52 (1H, s, -CO-*NH*-CH_2-), 8.17 (1H, s, -CO-*NH*-N-), 5.44 (1H, d, J=4.7 Hz, -C*H*), 5.24 (1H, s, -CO-*CH*-C-), 5.16 (1H, d, J=4.8 Hz, -C*H*). MS (M^+): 685.19.

Ethyl2-(2-(1-(2-(3-chloro-2-(2-hydroxyphenyl)-4-oxoazetidin-1-yl)benzoyl)-2-isonicotinoylhydrazinyl)-2-(3-nitrophenyl)acetamido)acetate (9d)

FTIR: 3450 (-OH), 3300 (-NH), 3115 (-CH, Ar), 1781 (-C=O, β-lactam). ^{1}H NMR: 11.27 (1H, s, -OH), 8.52 (1H, s, -CO-*NH*-CH_2-), 8.18 (1H, s, -CO-*NH*-N-), 5.44 (1H, d, J=4.7 Hz, -C*H*), 5.25 (1H, s, -CO-*CH*-C-), 5.14 (1H, d, J=4.8 Hz, -C*H*). MS (M^+): 700.17.

Ethyl2-(2-(1-(2-(3-chloro-2-(2-hydroxyphenyl)-4-oxoazetidin-1-yl)benzoyl)-2-isonicotinoylhydrazinyl)-2-(2-chloroquinolin-3-yl)acetamido)acetate (9e)

FTIR: 3451 (-OH), 3310 (-NH), 3120 (-CH, Ar), 1781 (-C=O, β-lactam). ^{1}H NMR: 11.24 (1H, s, -OH), 8.53 (1H, s, -CO-*NH*-CH_2-), 8.18 (1H, s, -CO-*NH*-N-), 5.44 (1H, d, J=4.7 Hz, -C*H*), 5.26 (1H, s, -CO-*CH*-C-), 5.16 (1H, d, J=4.8 Hz, -C*H*). MS (M^+): 740.16.

Ethyl2-(2-(1-(2-(3-chloro-2-(2-hydroxyphenyl)-4-oxoazetidin-1-yl)benzoyl)-2-isonicotinoylhydrazinyl)-2-(4-chlorophenyl)acetamido)acetate (9f)

FTIR: 3450 (-OH), 3318 (-NH), 3122 (-CH, Ar), 1780 (-C=O, β-lactam). ^{1}H NMR: 11.29 (1H, s, -OH), 8.54 (1H, s, -CO-*NH*-CH_2-), 8.15 (1H, s, -CO-*NH*-N-), 5.44 (1H, d, J=4.7 Hz, -C*H*), 5.26 (1H, s, -CO-*CH*-C-), 5.18 (1H, d, J=4.8 Hz, -C*H*). MS (M^+): 689.14.

(iv) Protocol for in vivo anti-inflammatory investigation of compounds 9(a-f)

The activity was evaluated by carrageenin induced rat paw oedema model[35]. Wistar albino rats of either sex weighing between 150-250g were used. Rats were divided into eight groups of six animals each. Rats belonging to Group I was control which was administered with normal saline water. Group II rats were administered with reference drug, ibuprofen at 10mg/kg. Group III, IV, V, VI, VII, and VIII rats were administered with test compounds 9(a-f) at 250mg/kg of body weight respectively. Freshly prepared 0.1ml carrageenin was injected into the left hind limb of each rat under the subplantar aponeurosis after one hour of oral administration of test compounds and ibuprofen. Increase in paw volume was measured by using plethysmometer. Paw volume was recorded at an interval of 0, 1, 2 and 3h after carrageenin injection. The data was statistically analyzed by one-way analysis of variance (ANOVA) where $P<0.05$ was considered as significantly different from control. The results were depicted in Table 1.

Table 1
Screening results of anti-inflammatory activity of compounds 9(a-f)

Test Compounds	Increase in paw volume at different time interval (h) (mean ± SEM)				% inhibition after 3h
	250 mg/kg				
	0	1	2	3	
Control	2.12 ± 0.07	2.41 ± 0.10	2.57 ± 0.12	2.63 ± 0.05	-
Ibuprofen (10mg/kg)	5.82 ± 0.10	9.11 ± 0.17*	14.61 ± 0.05	25.18 ± 0.11	82.73
9a	3.42 ± 0.04*	7.27 ± 0.11	9.36 ± 0.10	13.88 ± 0.06	68.32
9b	3.34 ± 0.15	5.16 ± 0.02*	8.07 ± 0.12	10.42 ± 0.18*	50.93
9c	3.30 ± 0.20	6.71 ± 0.14*	9.15 ± 0.12	15.34 ± 0.07*	67.29
9d	3.29 ± 0.05	6.57 ± 0.10	9.02 ± 0.05*	13.74 ± 0.20	54.64
9e	3.76 ± 0.21	7.31 ± 0.02*	10.04 ± 0.20	18.34 ± 0.17	68.78
9f	3.65 ± 0.08*	6.15 ± 0.04	8.74 ± 0.11	11.51 ± 0.15	52.46

Significantly different from control at P < 0.05.

(v) Protocol for in vitro anti-bacterial investigation of compounds 9(a-f)

The compounds were screened against Gram-negative (*Proteus mirabilis* and *Escherichia coli)* and Gram-positive *(Sterptococcus pnuemoniae* and *Bacillus cereus)* bacteria using well diffusion method. Amoxicillin was used as positive and ethanol as negative control. The test compounds and amoxicillin (5mg) was dissolved in ethanol (5ml, 1000µg/ml). Sample size was fixed at 0.1ml. The Petri dishes and nutrient agar medium was sterilized in autoclave. After sterilization, petri plates of agar medium were prepared by pouring melted agar inoculated with one day old above mentioned bacterial strains. Wells were scooped out from agar medium contained in sterilized petri plates. The test

compounds and amoxicillin were added in wells aseptically and incubated at 37°C for 24h. A clear zone of inhibition developed by each compounds was measured and compared with negative and positive control. The results were tabulated in Table 2.

Table 2
Screening results of antibacterial activity of compounds 9(a-f)

Compounds	Gram-negative		Gram-positive	
	P. mirabilis	*E. coli*	*S. pneumoniae*	*B. cereus*
Amoxicillin	+++	+++	+++	+++
9a	++	+++	+++	++
9b	++	++	+	++
9c	++	+++	++	+++
9d	+++	++	+++	++
9e	++	+++	+++	++
9f	+++	++	++	++

Inactive = - (inhibition zone < 5 mm); slightly active = + (inhibition zone 5-10 mm); moderately active = + + (inhibition zone 10-15 mm); highly active = + + + (inhibition zone > 15 mm).

RESULTS AND DISCUSSION

In this research article, a three step, one pot synthesis of Ugi derived β-lactam derivatives have been executed efficiently. It has been reported that few β-lactam derivatives have demonstrated a wide range of pharmacological activities including anti-inflammatory[36]. Keeping up with this fact, we have tested this activity on the synthesized derivatives. The drug dose for all compounds has been determined as per ED_{50}. Ibuprofen usual dosage are 200-400mg for adults and the effective dose value of compounds 9(a-f) were found to be 250mg/kg. Therefore reference has been selected by deducing drug dose in close proximity of an effective dose of synthesized compounds. Also ibuprofen has been used to lower high body temperature thereby possessing antipyretic activity. A non-steroidal anti-inflammatory medicines (NSAIMs) shows analgesics, antipyretic and predominantly anti-inflammatory effects by selective inhibition of cyclooxygenase enzyme (COX-1) and cyclooxygenase enzyme (COX-2). With respect to ibuprofen, compounds 9a, 9c and 9e are effective inhibiting inflammation whereas compounds 9b, 9d and 9f have shown moderate activity with respect to ibuprofen. It is probable that the biological activity of organic heterocyclic compounds depends upon functional group attached to the parent or adjacent ring. It is quite apparent that $–OCH_3$ group at meta or para, $-NO_2$ group at meta, -HO group at para positions in the same or in the second ring promotes biological applications. Nevertheless compounds 9(a-f) have inhibited inflammation up to 50-68% whereas ibuprofen has reduced inflammation about 82.73% in the same duration of time. It was considered that the novel Ugi derivatives might treats pain by blocking COX-2 in central nervous system (CNS). For antibacterial screening, minimum inhibitory concentration (MIC) in µg/ml was determined by the serial dilution method[37]. Amoxicillin has been selected as reference drug due to its potentiality to fight against various Gram-negative and positive bacteria and shows a broad zone of inhibition. It is evident from Table 2, compounds 9(a-f) posses moderate to highly active antibacterial effects. All compounds 9(a-f) have shown zone of inhibition more than 15mm except compound 9b which shows zone of inhibition around 10-15 mm.

CONCLUSION

In conclusion, a one-pot, three-step benign synthesis of β-lactam has been achieved successfully by using Ugi-4CR. The catalyst used in the reaction was eco-friendly and reusable. The anti-inflammatory screening results reveal that compounds 9a, 9c and 9e were found to possess good effects on inflammation with reference to ibuprofen. The antibacterial screening results reveal that compounds 9a, 9c, 9d, 9e and 9f were found to be potential antibacterial agents with respect to reference antibiotics. The overall reaction time to perform synthesis was approximately 6-10h. Further studies may have to follow up with the improved methodology with less reaction time and using more feasible combinatorial synthesis for the generation of more effective medicinal agents.

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CONFLICT OF INTEREST

Conflict of interest declared none.

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