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Synthesis of Novel Anti-Inflammatory and Antimicrobial Agents via Ugi-4CR and its Evaluation

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ABSTRACT

An efficient and rapid synthesis of novel anti-inflammatory and antimicrobial agents using 4-aminoantipyrine, nicotinic acid, ethylisocyanoacetate and substituted aldehydes via Ugi four component reaction (Ugi-4CR) protocol under microwave irradiation in presence of Fluorite as an efficient catalyst. The microwave synthesis route afforded better yields with shorter reaction time. The novel heterocycles were characterized on the basis of IR, ^{1}H NMR and Mass spectral analysis. All the synthesized molecules 5 (a-h) were examined for their potential in-vivo Anti-inflammatory activity on Wistar Albino rats using a standard reference drug, Indometacin. The synthesized compounds were also screened for their potent in-vitro Antimicrobial activity using few Gram-positive and Gram-negative bacteria against a reference antibiotic, Ampicillin and Streptomycin.

INTRODUCTION

Inflammation is a tissue-reaction to infection, irritation or foreign substance. It is a part of the host defence mechanism in order to eliminate or limit the spread of injurious agents. There are various components to an inflammatory reaction such as oedema formation, leukocyte infiltration and granuloma (Mitchell and Cotron, 2010). The research on nicotinic acid revealed that the related derivatives possess wide range of therapeutic application such as anti-inflammatory (Kalia *et al*., 2007), antimicrobial (Yeong *et al*., 2004), antimycobial (Gabriel *et al*., 2007), anticancer (Boovanahalli *et al*., 2007), antiviral (Pandey *et al*., 2005), antiatherogenic (Holzhauser *et al*., 2011) and antioxidant activity (Spanou *et al*., 2007). Similarly, Pyrazolone and its derivatives such as 4-aminoantipyrine have shown various biological applications such as anti-inflammatory (Costa *et al*., 2006), analgesic (Burdulene *et al*., 1999), antiviral (Evstropov *et al*., 1992), antipyretic, antirheumatic and antimicrobial activity (Ei Ashry *et al*., 2007). The versatile applications of nicotinic acid and 4-aminoantipyrine have given interest to design and synthesize a novel derivatives using combinatorial chemistry (Pandeya and Thakkar, 2005). Hence we have condensed 4-aminoantipyrine and nicotinic acid in a four component Ugi reaction for their pharmaceutical applications. Microwave mediated multicomponent reactions constitute an especially attractive synthetic strategy for rapid and efficient library generation due to the fact that the products are formed in a single step and diversity can be achieved simply by varying the reacting components (Quiroga *et al*., 2001). Among many kinds of multicomponent condensations, the Ugi reaction (Ugi, 1962) is highly convergent for the rapid generation of organic drug-like molecule libraries and many different types of biologically active targets (Domling and Ugi, 2000). The Ugi-4CR in which an amine, an aldehyde or ketone, a carboxylic acid, and an isocyanide combine to yield α-*N*-acylaminoamide (Kim *et al*., 2001) is particularly attractive because of the wide range of products obtainable through variation of the starting materials. Ugi reactions have been performed using various catalysts (Hugel, 2009). However, some of the reported synthesis consists of lesser yields with more reaction time. Therefore we have employed Fluorite (Chitra and Pandiarajan, 2009; Wada and Suzuki, 2003), a natural occurring halide mineral composed of calcium fluoride (CaF_2) as a catalyst to overcome the drawback of time and yield.

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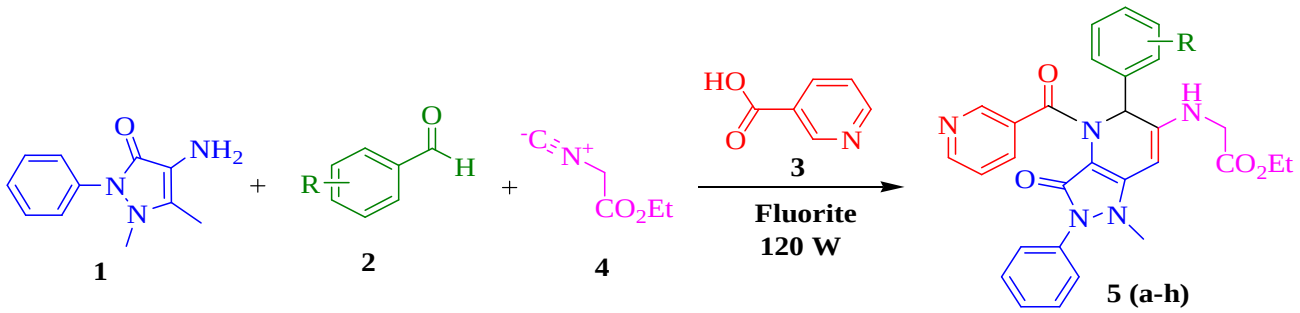

Where R= 3-NO_2, 2-NO_2, 4-$N(Me)_2$, 4-OMe, 2-OH, 4-OH, 2-Cl, 4-Cl

Scheme 1: Synthesis of Ugi-4CR under microwave irradiation.

In view of the remarkable importance from the pharmacological, industrial and synthetic point, herein we wish to report a novel one-pot synthesis of anti-inflammatory and antimicrobial agents via Ugi-4CR under microwave irradiation using Fluorite as an efficient catalyst within the framework of green chemistry protocol. The experimental protocol was approved by Institutional Animal Ethical Committee (IAEC) as per the guidelines of Committee for the Purpose of Control and Supervision of Experiments on Animals (CPCSEA), Ministry of Social Justice and Empowerment, Government of India. (Grant No. SPCP/2013/595).

MATERIALS AND METHODS

All reagents and solvents are of analytical grade and used directly. All melting points were determined by open tube capillaries method and are uncorrected. The microwave (MW) reactions were carried out in CEM – 908010, bench mate model, 300W laboratory MW reactor. IR spectra (υ_{max} in cm^{-1}) were recorded on Schimadzu-IR Prestige 21spectrophotometer using KBr technique. ^{1}H NMR spectra were recorded on Bruker-Avance (400 MHz), spectrophotometer using DMSO-d_6 solvent and TMS as an internal standard. Mass spectra were recorded on Waters Micromass Q-T of micro spectrometer. Antimicrobial screening was carried out at Department of Biotechnology, Sindhu Mahavidyalaya, Nagpur, India.

Protocol for the synthesis of Ugi-4CR derivatives 5(a-h)

A mixture of 4-aminoantipyrine (0.01 mol), substituted aldehydes (0.01 mol), ethylisocyanoacetate (0.01 mol), and nicotinic acid (0.01 mol) was dissolved in 5 ml of 95% ethanol and Fluorite (2% weight with respect to all reactants) was taken in a conical flask capped with a funnel and irradiated under microwave at 120 W **(Scheme 1)**. The completion of the reaction was monitored by TLC (0.5mm thickness) using silica gel-G coated Al-plates (Merck) by using mixture of ethyl acetate and hexane as mobile phase and spots were visualized by exposing the dry plates in iodine vapours. After completion, the reaction mixture was allowed to attain room temperature. The crude product and catalyst was collected by filtration. The crude product was purified by recrystallization from hot ethanol.

Ethyl 2-(1-methyl-4-nicotinoyl-5-(3-nitrophenyl)-3-oxo-2-phenyl-2,3,4,5-tetrahydro-1H-pyrazolo[4,3-b]pyridin-6-ylamino) acetate (5a)

93%. Yellow crystals; m.p. 145-147°C; FT-IR (KBr, cm^{-1}): 3410 (N-H), 3044-3073 (Ar-CH), 1715 (C=O), 1550 (NO_2), 1456 (C=N), 1290 (C-N); ^{1}H NMR (400 MHz, DMSO d_6) δ/ppm: 2.15 (br, s, 1H, -NH), 5.35 (s, 1H, -CH), 4.86 (s, 1H, -CH), 2.96 (s, 3H, $-CH_3$), 3.58 (s, 1H, $-CH_2$), 4.18 (q, 2H, $-CH_2$), 1.36 (t, 3H, $-CH_3$), 6.71-7.45 (m, 13H, Ar-H); Anal. Calcd: $C_{29}H_{26}N_6O_6$; Mass spectra m/z = 554.19 (100%).

Ethyl 2-(1-methyl-4-nicotinoyl-5-(2-nitrophenyl)-3-oxo-2-phenyl-2,3,4,5-tetrahydro-1H-pyrazolo[4,3-b]pyridin-6-ylamino) acetate (5b)

87%. Pale yellow crystals; m.p. 142-144°C; FT-IR (KBr, cm^{-1}): 3422 (N-H), 3040-3072 (Ar-CH), 1712 (C=O), 1547 ($-NO_2$), 1455 (C=N), 1291 (C-N); ^{1}H NMR (400 MHz, DMSO d_6) δ/ppm: 2.18 (br, s, 1H, -NH), 5.31 (s, 1H, -CH), 4.88 (s, 1H, -CH), 2.93 (s, 3H, $-CH_3$), 3.61 (s, 1H, $-CH_2$), 4.12 (q, 2H, $-CH_2$), 1.38 (t, 3H, $-CH_3$); 6.74-7.48 (m, 13H, Ar-H); Anal. Calcd: $C_{29}H_{26}N_6O_6$; Mass spectra m/z = 554.19 (100%).

Ethyl 2-(1-methyl-4-nicotinoyl-5-(4-(dimethylamino)phenyl)-3-oxo-2-phenyl-2,3,4,5-tetrahydro-1H-pyrazolo [4,3-b]pyridin-6-ylamino)acetate (5c)

78%. Maroon crystals; m.p. 156-158°C; FT-IR (KBr, cm^{-1}): 3414 (N-H), 3051-3083 (Ar-CH), 1725 (C=O), 1458 (C=N), 1285 (C-N); ^{1}H NMR (400 MHz, DMSO d_6)δ/ppm: 2.12 (br, s, 1H, -NH), 3.08 (s, 6H, $N(CH_3)_2$), 5.36 (s, 1H, -CH), 4.86 (s, 1H, -CH), 2.55 (s, 3H, $-CH_3$), 3.57 (s, 1H, $-CH_2$), 4.16 (q, 2H, $-CH_2$), 1.35 (t, 3H, $-CH_3$); 6.67-7.34 (m, 13H, Ar-H); Anal. Calcd: $C_{31}H_{32}N_6O_4$; Mass spectra m/z = 552.25 (100%).

Ethyl 2-(1-methyl-4-nicotinoyl-5-(4-methoxyphenyl)-3-oxo-2-phenyl-2,3,4,5-tetrahydro-1H-pyrazolo[4,3-b]pyridin-6-ylamino) acetate (5d)

88%. Yellow crystals; m.p. 148-150°C; FT-IR (KBr, cm^{-1}): 3420 (N-H), 3056-3068 (Ar-CH), 2832 ($-OCH_3$), 1720 (C=O), 1454 (C=N), 1290 (C-N); ^{1}H NMR (400 MHz, DMSO d_6)δ/ppm: 2.16 (br, s, 1H, -NH), 5.38 (s, 1H, -CH), 4.87 (s, 1H, -CH), 3.75 (s, 3H, $-CH_3$), 2.51 (s, 3H, $-CH_3$), 3.63 (s, 1H, $-CH_2$), 4.15 (q, 2H, -

CH_2), 1.36 (t, 3H, -CH_3); 6.68-7.52 (m, 13H, Ar-H); Anal. Calcd: $C_{30}H_{29}N_5O_5$; Mass spectra m/z = 539.22 (100%).

Ethyl 2-(1-methyl-4-nicotinoyl-5-(2-hydroxyphenyl)-3-oxo-2-phenyl-2,3,4,5-tetrahydro-1H-pyrazolo[4,3-b]pyridin-6-ylamino) acetate (5e)

75%. Pale yellow crystals; m.p. 165-167^oC; FT-IR (KBr, cm^{-1}): 3418 (N-H), 3063-3077 (Ar-CH), 3347 (O-H), 1715 (C=O), 1456 (C=N), 1291 (C-N); ^1H NMR (400 MHz, DMSO d_6)δ/ppm: 2.15 (br, s, 1H, -NH), 5.36 (s, 1H, -CH), 4.84 (s, 1H, -CH), 2.53 (s, 3H, -CH_3), 3.58 (s, 1H, -CH_2), 4.22 (q, 2H, -CH_2), 1.35 (t, 3H, -CH_3); 6.81-7.62 (m, 13H, Ar-H); Anal. Calcd: $C_{29}H_{27}N_5O_5$; Mass spectra m/z = 554.19 (100%).

Ethyl 2-(1-methyl-4-nicotinoyl-5-(4-hydroxyphenyl)-3-oxo-2-phenyl-2,3,4,5-tetrahydro-1H-pyrazolo[4,3-b]pyridin-6-ylamino) acetate (5f)

90%. Pale yellow crystals; m.p. 152-154^oC; FT-IR (KBr, cm^{-1}): 3428 (N-H), 3051-3073 (Ar-CH), 3367 (O-H), 1718 (C=O), 1454 (C=N), 1293 (C-N); ^1H NMR (400 MHz, DMSO d_6)δ/ppm: 2.21 (br, s, 1H, -NH), 5.37 (s, 1H, -CH), 4.88 (s, 1H, -CH), 2.59 (s, 3H, -CH_3), 3.58 (s, 1H, -CH_2), 4.18 (q, 2H, -CH_2), 1.35 (t, 3H, -CH_3); 6.73-7.55 (m, 13H, Ar-H); Anal. Calcd: $C_{29}H_{27}N_5O_5$; Mass spectra m/z = 525.21 (100%).

Ethyl 2-(1-methyl-4-nicotinoyl-5-(3-chlorophenyl)-3-oxo-2-phenyl-2,3,4,5-tetrahydro-1H-pyrazolo[4,3-b]pyridin-6-ylamino) acetate (5g)

87%. Pale yellow crystals; m.p. 161-163^oC; FT-IR (KBr, cm^{-1}): 3426 (N-H), 3044-3064 (Ar-CH), 1722 (C=O), 1455 (C=N), 1290 (C-N), 781 (C-Cl); ^1H NMR (400 MHz, DMSO d_6)δ/ppm: 2.15 (br, s, 1H, -NH), 5.33 (s, 1H, -CH), 4.86 (s, 1H, -CH), 2.63 (s, 3H, -CH_3), 3.65 (s, 1H, -CH_2), 4.17 (q, 2H, -CH_2), 1.38 (t, 3H, -CH_3); 6.84-7.63 (m, 13H, Ar-H); Anal. Calcd: $C_{29}H_{26}ClN_5O_4$; Mass spectra m/z = 543.17 (100%).

Ethyl 2-(1-methyl-4-nicotinoyl-5-(4-chlorophenyl)-3-oxo-2-phenyl-2,3,4,5-tetrahydro-1H-pyrazolo[4,3-b]pyridin-6-ylamino) acetate (5h)

77%. Yellow crystals; m.p. 172-174^oC; FT-IR (KBr, cm^{-1}): 3418 (N-H), 3038-3074 (Ar-CH), 1717 (C=O), 1456 (C=N), 1291 (C-N), 775 (C-Cl); ^1H NMR (400 MHz, DMSO d_6)δ/ppm: 2.20 (br, s, 1H, -NH), 5.32 (s, 1H, -CH), 4.85 (s, 1H, -CH), 2.65 (s, 3H, -CH_3), 3.67 (s, 1H, -CH_2), 4.21 (q, 2H, -CH_2), 1.35 (t, 3H, -CH_3); 6.73-7.68 (m, 13H, Ar-H); Anal. Calcd: $C_{29}H_{26}N_6O_6$; Mass spectra m/z = 543.17 (100%).

In-Vivo Anti-inflammatory Activity

Winter *et al*., 1962, method was used to induce inflammation by injecting carrageenin in hind paw of Wistar Albino rats. Rats of either sex weighing between 150-200 g were used for the present study and divided into eight groups of six animals each. After one hour of the oral administration of synthesized drugs (200 and 400 mg/kg) and reference drug (Indometacin, 10 mg/kg), freshly prepared 0.1ml carrageenin (1% carrageenin in 0.9% NaCl) was injected into the left hind limb of each rat under the subplantar aponeurosis. Measurement of paw volume was done by means of volume displacement technique using Plethysmometer (Bhatt *et al*., 1977).

Paw volume was recorded at the interval of 0, 1, 3 and 5h after carrageenin injection. Results were expressed as an increase in paw volume in comparison to the initial paw volumes and in comparison with control group. All the results were expressed as mean ± S.E.M. The data were statistically analyzed by one-way analysis of variance (ANOVA) and P<0.05 were considered as significant.

Table 1: Anti-inflammatory activity of compounds **5 (a-h)** against carrageenin-induced paw oedema in Wistar Albino rats.

Test Compounds	% Inhibition of paw oedema at different time (h) interval[a]							
	200 mg/kg				400 mg/kg			
	0	1	3	5	0	1	3	5
Control[b]	1.43 ± 0.15 (0.0)	1.46 ± 0.11 (0.0)	1.52 ± 0.14 (0.0)	1.48 ± 0.13 (0.0)	1.45 ± 0.12 (0.0)	1.47 ± 0.14 (0.0)	1.54 ± 0.15 (0.0)	1.46 ± 0.12 (0.0)
5a	1.13 ± 0.04 (34.08)	1.16 ± 0.15 (26.81)	1.18 ± 0.08 (56.15)	1.17 ± 0.03* (65.28)	1.19 ± 0.02* (45.07)	1.15 ± 0.13 (71.08)	1.17 ± 0.11* (60.22)	1.16 ± 0.12 (74.21)
5b	1.24 ± 0.14 (10.21)	1.25 ± 0.19 (16.12)	1.27 ± 0.21 (46.11)	1.23 ± 0.04 (55.13)	1.26 ± 0.01 (42.13)	1.28 ± 0.05 (32.06)	1.32 ± 0.09 (57.11)	1.25 ± 0.03* (54.03)
5c	1.34 ± 0.01* (16.27)	1.35 ± 0.04 (26.51)	1.38 ± 0.06* (33.17)	1.28 ± 0.06* (46.21)	1.33 ± 0.01* (23.12)	1.37 ± 0.02* (32.28)	1.40 ± 0.05 (54.17)	1.34 ± 0.03* (47.15)
5d	1.17 ± 0.04 (30.31)	1.18 ± 0.07 (56.27)	1.19 ± 0.03 (54.32)	1.16 ± 0.08 (64.52)	1.28 ± 0.03 (36.25)	1.34 ± 0.04 (60.21)	1.42 ± 0.02 (72.05)	1.38 ± 0.06 (76.18)
5e	1.37 ± 0.04 (16.05)	1.38 ± 0.07 (23.07)	1.44 ± 0.13 (40.05)	1.35 ± 0.07 (55.13)	1.37 ± 0.01* (18.03)	1.39 ± 0.02* (35.07)	1.42 ± 0.04 (53.13)	1.38 ± 0.05* (24.16)
5f	1.12 ± 0.02* (32.06)	1.14 ± 0.06 (34.13)	1.16 ± 0.09 (58.04)	1.15 ± 0.05 (67.05)	1.18 ± 0.12 (40.62)	1.21 ± 0.15 (70.21)	1.24 ± 0.03 (68.18)	1.20 ± 0.11 (74.08)
5g	1.31 ± 0.06 (13.09)	1.33 ± 0.04 (33.06)	1.42 ± 0.05 (40.02)	1.36 ± 0.06* (50.05)	1.28 ± 0.13* (38.02)	1.25 ± 0.014 (25.15)	1.42 ± 0.07 (36.17)	1.48 ± 0.15 (53.04)
5h	1.12 ± 0.16 (33.14)	1.14 ± 0.04 (47.23)	1.15 ± 0.06* (57.11)	1.13 ± 0.12 (70.21)	1.22 ± 0.01* (40.13)	1.25 ± 0.03* (71.32)	1.32 ± 0.13 (66.57)	1.30 ± 0.05 (75.31)
Indometacin (10 mg/kg)	1.08 ± 0.06* (70.43)	1.09 ± 0.02* (75.26)	1.13 ± 0.02* (77.22)	1.12 ± 0.03* (81.56)	-	-	-	-

*Significantly different from control at P < 0.05.

[a] Results are expressed as mean ± SEM and compared with student "t" test.

[b] The group was injected with 1 ml of 0.5% aqueous saline water.

In-Vitro Antimicrobial Activity

The synthesized compounds **5 (a-h)** were screened for antibacterial activities against *Staphylococcus aureus* (Gram-positive), *Bacillus subtilis* (Gram-positive), *Escherichia coli* (Gram-negative) and *Klebsiella pneumoniae* (Gram-negative) using well diffusion method. Ampicillin and Streptomycin were used as standard drugs and ethanol was used as negative control. Each test compound (5 mg) was dissolved in ethanol (5 ml, 1000 µg/ml), which was used as sample solution. Sample size for all the compounds was fixed at 0.1 ml. The cultures of above bacterial strains were inoculated in 10 ml nutrient broth and incubated at 37^{o}C for 24 hrs. The Petri dishes and nutrient agar medium was sterilized by autoclaving. To this sterilized nutrient medium 1 ml of one day old bacterial culture was added and spread over the Petri plate. The wells impregnated with 1000µg/ml of newly synthesized compounds were introduced aseptically in the nutrient agar plate. All the nutrient agar plates were incubated at 37^{o}C for 24 hrs after which the plates were observed for clear zone of inhibition.

Table 2: Antimicrobial activity of compounds **5 (a-h).**

Compounds	Gram-positive bacteria		Gram-negative bacteria	
	S. aureus	*B. subtilis*	*E. coli*	*K. pneumoniae*
5a	++	++	+++	+
5b	-	++	-	+
5c	++	+	+	-
5d	++	++	++	+
5e	+	-	+	+
5f	++	+	++	++
5g	++	++	++	+
5h	+	++	+	+
Ampicillin	+++	++	+++	++
Streptomycin	+++	+++	+++	+++

Key to symbols: 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 the present study, we report the condensation of 4-aminoantipyrine, nicotinic acid, ethylisocyanoacetate and substituted aldehydes via Ugi-4CR protocol under microwave irradiation in presence of Fluorite as a catalyst **(Scheme 1)**. Fluorite acts as a mild acid in the dehydration reaction and increase the reaction rate without affecting the yield of desired products. It is significant to note that the catalytic amount of Fluorite accomplishes the reaction successfully and the use of microwave energy further enhances the yields of the product with reduction in time. Yields of 75-93% were achieved in 10-15 min of microwave irradiation. The catalyst was easily isolated after the completion of reaction and was reused in at least eight reactions. All synthesized compounds were evaluated by ^{1}H NMR, I.R, and mass spectral analysis. In-vivo anti-inflammatory screening results were summarized in **Table 1.** In case of compound **5a,** at 3h for 200mg/kg drug dose, % inhibition of paw oedema has increased up to 56.15% while for 400mg/kg drug dose, 60.22% of inhibition of paw oedema was increased. Moreover, at 5h for 200mg/kg, % inhibition of paw oedema has been increased till 65.28% while for 400mg/kg, 74.12% of inhibition was increased. In general, an increase in % inhibition of paw oedema was observed as time interval increases for all the synthesized compounds. Hence, it is evident from **Table 1** that compounds **5a, 5d, 5f** and **5h** showed effective activity when compared with the standard drug, Indometacin. The screening results of in-vitro antimicrobial activity showed a broad spectrum for compounds **5a, 5d, 5f** and **5g** when compared with standard reference drug Ampicillin and Streptomycin. On the contrary compounds **5b, 5c, 5e** and **5h** showed moderate to slightly active against the used strains described in **Table 2**. On the basis of screening data obtained from in-vivo and in-vitro studies, we have concluded that the synthesized moieties are equipotent anti-inflammatory and antimicrobial agents.

CONCLUSION

In this paper, we have studied in-vivo and in-vitro anti-inflammatory and antimicrobial activities respectively of the synthesized moieties from one-pot microwave mediated Ugi-4CR with good to excellent yields in a green chemical pathway. This study reveals that the synthesized moieties possess potential anti-inflammatory and antimicrobial activities. Furthermore, utility, no toxicity, reusability, low cost, and ease of isolation after completion of reaction are the remarkable features of the catalyst.

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REFERENCES

Bhatt K R., Mehta R K., Srivastava PN. Simple methods for recording anti-inflammatory effect on rat paw oedema. Indian Journal of Physiology and Pharmacology. 1977; (21):399-400.

Boovanahalli SK., Jin X., Jin Y., Kim JH., Dat NT., Hong YS., Lee JH., Jung SH., Lee K., Lee JJ. Synthesis of (aryloxyacetylamino)-isonicotinic/nicotinic acid analogues as potent hypoxia inducible factor (HIF)-1α inhibitors. Bioorganic & Medicinal Chemistry Letters. 2007; (17):6305-10.

Burdulene D., Palaima A., Stumbryavichyute Z., Talaikite Z. Synthesis and antiinflammatory activity of 4-aminoantipyrine derivatives of succinamides. Pharmaceutical Chemistry Journal. 1999; 33:191-193.

Chitra S., Pandiarajan K. Calcium fluoride: an efficient and reusable catalyst for the synthesis of 3,4-dihydropyrimidin-2(1H)-ones and their corresponding 2(1H)thione: an improved high yielding protocol for the Biginelli reaction. Tetrahedron Letters. 2009; (50):2222–2224.

Costa D., Marques AP., Reis R L., Lima JLFC., Fernandes E. Inhibition of human neutrophil oxidative burst by pyrazoline derivatives. Free Radical Biology Medicine. 2006, 40:632-640.

Domling A., Ugi I. Multicomponent reactions with isocyanides. Angewandte Chemie International Edition. 2000; (39):3168-3210.

Evstropov AN., Yavorovskaya VE., Vorobev ES., Khudonogova ZP., Gritsenko LN., Shmidt EV., Medvedeva SG., Filimonov VD., Prishchep TP., Saratikov AS. Synthesis and antiviral activity of antipyrine derivatives. Pharmaceutical Chemistry Journal. 1992; (26):426-430.

Ei Ashry ESH., Awad LF., Ibrahim EI., Bdeewy OK. Synthesis of antipyrine derivatives derived from dimedone. Chinese Journal of Chemistry. 2007; 25(4):570-573.

Gabriel NV., Gloria MS., Zetel DF., Javier VV., Samuel ES. Synthesis and antimycobacterial activity of 4-(5-substituted-1,3,4-oxadiazol-2-yl)pyridines. Bioorganic & Medicinal Chemistry. 2007; 15 (16):5502-5508.

Holzhauser E., Albrecht CM., Zhou Q., Buttler A., Preusch MR., Blessing E., Katus HA., Bea F. Nicotinic acid has anti-atherogenic and anti-inflammatory properties on advanced atherosclerotic lesions independent of its lipid-modifying capabilities. Journal of Cardiovascular Pharmacology. 2011; 57 (4):447-454.

Hugel HM. Microwave multicomponent synthesis. Molecules. 2009; (14):4936-4972.

Kalia R., Rao CM., Kutty NG. Synthesis and evaluation of the antiinflammatory activity of N-[2-(3,5-Ditert-butyl-4-hydroxyphenyl)-4-oxothiazolidin-3-yl]-nicotinamide. Arzneimittel-Forschung-Drug Research. 2007; 57(9):616-622.

Kim YB., Choi EH., Keum G., Kang SB., Lee DH., Koh HY., Kim Y. An efficient synthesis of morpholin-2-one derivatives using glycolaldehyde dimer by the Ugi multicomponent reaction. Organic Letters. 2001; (3):4149-4152.

Mitchell RN., Cotron RS. Robinsons Basic Pathology, seventh edition, Harcourt Pvt. Ltd; New Delhi, India, 2010; 34-42.

Pandeya S N., Thakkar D. Combinatorial Chemistry: A novel method in drug discovery and its application, Indian Journal of Chemistry. 2005; (44B):158-162.

Pandey VK., Gupta VD., Upadhyay M., Upadhyay M., Singh VK., Tandon M. Synthesis, Characterization and biological activities of 1,3,4-substituted 2-azetidinones. Indian Journal of Chemistry. 2005; (44B):158-162.

Quiroga J., Cisneros C., Insuasty B., Abonia R., Nogueras M., Sanchez A. A regiospecific three-component one-step cyclocondensation to 6-cyano-5,8-dihydropyrido[2,3-d]pyrimidin-4(3H)-ones using microwaves under solvent-free conditions. Tetrahedron Letters. 2001; (42):5625–5627.

Spanou C., Manta S., Komiotis D., Dervishi A., Kouretas D. Antioxidant activity of a series of fluorinated pyrano-nucleoside analogues of N^4-benzoyl cytosine and N^6-benzoyl adenine. International Journal of Molecular Science. 2007; 8:695-704.

Ugi I. The α-addition of immonium ions and anions to isonitriles accompanied by secondary reactions. Angewandte Chemie International Edition. 1962; 1:8-21.

Wada S., Suzuki H. Calcite and fluorite as catalyst for the Knovenagel condensation of malononitrile and methyl cyanoacetate under solvent-free conditions. Tetrahedron Letters. 2003; (44):399-401.

Winter CA., Risley EA., Nuss GW. Carrageenin-induced edema in hind paw of the rats as an assay for anti-inflammatory drugs. Proceedings of the Society for Experimental Biology and Medicine. 1962; (3):544-547.

Yeong WJ., Weon BI., Jae KR., Mi JS., Won BK., Eung CC. Synthesis and antibacterial activity of oxazolidinones containing pyridine substituted with heteroaromatic ring. Bioorganic & Medicinal Chemistry. 2004; 12(22):5909-5915.

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