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EVALUATION OF ANALGESIC AND ANTI-INFLAMMATORY ACTIVITIES OF SYNTHESIZED AGENTS USING UGI MULTICOMPONENT REACTION

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ABSTRACT: In the present study, analgesic and anti-inflammatory activities of the synthesized agents derived from Ugi four component reactions (Ugi-4CR) has been described. The synthesized novel Ugi derivatives **7 (a-h)** were characterized on the basis of I.R, ^{1}H NMR and mass spectral analysis. Healthy Wistar Albino rats were used to carry out these activities. Analgesic activity was evaluated by Eddy hot plate method using Morphine Sulfate as a standard reference drug. Anti-inflammatory activity was evaluated by mercury displacement method using Diclofenac as standard reference drug. The results were expressed as mean ± S.E.M. The data were statistically analyzed by Student's t test and $P<0.05$ were considered as significant. The screening data shows that synthesized compounds possess potential analgesic and anti-inflammatory activities.

INTRODUCTION: Mainly used non-steroidal anti-inflammatory drugs (NSAIDs) have limitations for therapeutic use since they cause gastrointestinal and renal side effects that are indivisible from their pharmacological activities.

Consequently, the synthesis of new compounds devoid of such side effects has become an important goal for medicinal chemists in recent years. For this purpose, various compounds incorporating a pyridazinone ring have been synthesized and their pharmacological activities have been reported [1, 2]. It has been reported that a considerable number of 3(2H)-pyridazinone derivatives bear analgesic activity.

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Among these compounds, Emorfazone is an analgesic and anti-inflammatory compound marketed as Pentoil and Nandron [3-5]. Rohet *et al*., reported the synthesis 3(2H)-pyridazinone derivatives were more potent than acetaminophen and noramidopyrine in a p-benzoquinone-induced writhing test [6].

In the quest of designing new agents effectively, multicomponent reactions have become one of the favoured methods to prepare pharmacologically relevant compounds. A multicomponent reaction (MCR) is a one-step reaction that combines two or more reagents to form an end product [7].

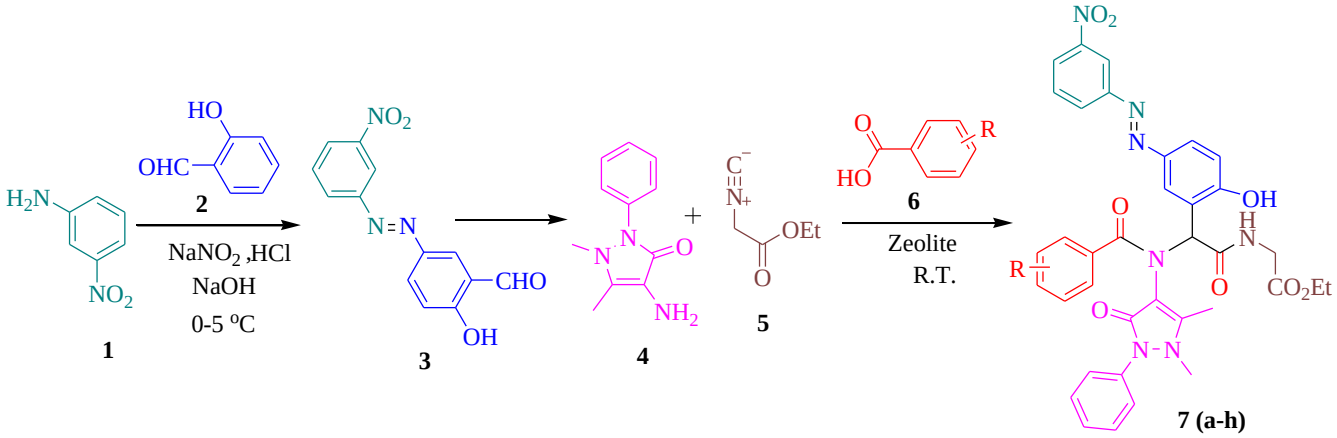
Among several MCRs, Ugi reaction [8] is highly convergent multicomponent used to synthesize heterocycles which are the most powerful tool for the rapid generation of organic drug-like molecules and to achieve many different types of biologically active targets [9]. The Ugi four component condensations in which an amine, an aldehyde or ketone, a carboxylic acid, and an isocyanide [10] combine to yield α-*N*-

acylaminoamide [11-13] is particularly interesting because of wide range of products obtainable through variation of starting materials [14]. Similarly, Pyrazolone and its derivatives such as 4-aminoantipyrine have shown various biological applications such as anti-inflammatory [15], analgesic [16], antiviral [17], antipyretic and antimicrobial activity [18]. The versatile applications of 4-aminoantipyrine have given interest to design and synthesize novel derivatives using combinatorial chemistry [19]. Hence we have condensed 4-aminoantipyrine in a four component Ugi reaction.

Herein, we wish to report a novel and biologically active agents synthesized from Ugi-4CR via azo linked dye using environmentally benign, commercially available and reusable Zeolite as a catalyst under ambient conditions in a green chemistry protocol. The experimental protocol was approved by Institutional Animal Ethics 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:

General: All reagents and solvents are of analytical grade purchased from a commercial source and used directly. All the melting points were determined by open tube capillaries method and are uncorrected. The purity of compounds was checked routinely by TLC using silica gel-G coated Al-plates (Merck) and spots were visualized by exposing the dry plates in iodine vapours. IR spectra were recorded on a Schimadzu-IR Prestige 21spectrophotometer using KBr technique; ^{1}H NMR spectra were recorded on a Bruker-Avance II (400 MHz) using DMSO-d_6 solvent and TMS as the internal standard. Mass spectra were recorded on Waters Micromass Q-T of micro spectrometer.



R= 3-NO_2, 4-NO_2, 2-Me, 4-Me, 2-Cl, 4-Cl, 2-OH, 4-OH

SCHEME 1: SYNTHESIS OF UGI-4CR DERIVATIVES

Synthesis of 2-hydroxy-4-((3-nitrophenyl) diazenyl)benzaldehyde (3): 3-Nitroaniline (1 mol) in dilute hydrochloric acid was diazotized with sodium nitrite (1 mol, 10 ml) solution at 0-5^{o}C with vigorous stirring. The resulting diazonium solution was poured drop wise with vigorous stirring to 2-hydroxy benzaldehyde (1 mol) containing 10% sodium hydroxide at 0-5^{o}C **(Scheme 1)**. The pH was maintained at 7.0 by simultaneous addition of 10% aqueous sodium hydroxide solution. After completion, the precipitate was collected by filtration and washed with 100 ml sodium chloride solution under vacuum. The resulting product was dried and crystallized from absolute ethanol. The following is the spectral data of the synthesized moiety.

Orange red solid; Yield 95%; m.p. 145-146^{o}C; FT-IR (KBr, cm^{-1}): 3398 (O-H), 1719 (C=O), 2820 (C-H), 863 (C-N), 1525 (N=O); ^{1}H NMR (400 MHz, DMSO d_6) δ/ppm: 4.32 (s, 1H, -OH), 10.34 (s, 1H, -CH), 7.24 -8.37 (m, 7H, Ar-H); Mass spectra: $C_{13}H_9N_3O_4$: m/z = 271.06 (100%).

Synthesis of Ugi-4CR (7a-h) using (3): A mixture of 2-hydroxy-4-((3-nitrophenyl)diazenyl)benzal dehyde **3** (0.1 mol), 4-aminoantipyrine **4** (0.1 mol), ethylisocyanoacetate **5** (0.1 mol), substituted carboxylic acid **6** (0.1 mol) in ethanol (10ml) and Zeolite in one-pot was magnetically stirred at room temperature **(Scheme 1)**.

The reaction mixture was stirred for 6-12h. The completion of the reaction was monitored by TLC. The crude product and catalyst was collected on a Buchner funnel by filtration. The crude product was purified by recrystallization from hot ethanol to get the pure product. All the products were characterized by IR, ^{1}H NMR and Mass spectra. The following are the spectral data of the synthesized Ugi derivatives.

Ethyl (5-(2-hydroxy-3-((3-nitrophenyl)diazenyl) phenyl)-1-methyl-4-(3-nitrobenzoyl)-3-oxo-2-phenyl-2,3,4,5-tetrahydro-1H-pyrazolo-pyridin-6-ylamino)acetate (7a): Pale yellow crystal; Yield 92%; m.p.: 164-165^{o}C; FT-IR (KBr, cm^{-1}): 3096 (N-H), 3065 (O-H), 1654 (C=O), 1530 (-NO_2), 1425 (N=N), 1281 (C-N); ^{1}H NMR (400 MHz, DMSO d_6): 2.0 (br, s, 1H, -NH), 5.13 (s, 1H, -OH), 3.61 (s, 2H, -CH_2), 2.46 (s, 3H, -CH_3), 4.15 (q, 2H, -CH_2), 1.33 (t, 3H, -CH_3), 5.56 (s, 1H, -CH); 6.72-8.44 (m, 16H, Ar-H); Mass spectra: $C_{36}H_{30}N_8O_9$: m/z = 718.22 (100%).

Ethyl (5-(2-hydroxy-3-((3-nitrophenyl)diazenyl) phenyl)-1-methyl-4-(4-nitrobenzoyl)-3-oxo-2-phenyl-2,3,4,5-tetrahydro-1H-pyrazolo-pyridin-6-ylamino)acetate (7b): Yellow crystal; Yield 90%; m.p.: 162-163^{o}C; FT-IR (KBr, cm^{-1}): 3095 (N-H), 3068 (O-H), 1655 (C=O), 1528 (-NO_2), 1425 (N=N), 1283 (C-N); ^{1}H NMR (400 MHz, DMSO d_6): 2.0 (br, s, 1H, -NH), 5.11 (s, 1H, -OH), 3.64 (s, 2H, -CH_2), 2.47 (s, 3H, -CH_3), 4.16 (q, 2H, -CH_2), 1.32 (t, 3H, -CH_3), 5.56 (s, 1H, -CH), 7.10-8.34 (m, 16H, Ar-H); Mass spectra: $C_{36}H_{30}N_8O_9$: m/z = 719 (100%).

Ethyl (5-(2-hydroxy-3-((3-nitrophenyl)diazenyl) phenyl)-1-methyl-4-(2-methylbenzoyl)-3-oxo-2-phenyl-2,3,4,5-tetrahydro-1H-pyrazolo-pyridin-6-ylamino)acetate (7c): Pale yellow crystal; Yield 85%; m.p.: 152-153^{o}C; FT-IR (KBr, cm^{-1}): 3094 (N-H), 3065 (O-H), 2853 (-CH_3), 1657 (C=O), 1536 (-NO_2), 1427 (N=N), 1281 (C-N); ^{1}H NMR (400 MHz, DMSO d_6): 2.0 (br, s, 1H, -NH), 5.0 (s, 1H, -OH), 3.61 (s, 2H, -CH_2), 2.47 (s, 3H, -CH_3), 4.12 (q, 2H, -CH_2), 1.30 (t, 3H, -CH_3), 5.56 (s, 1H, -CH), 2.35 (s, 3H, -CH_3), 7.18-8.39 (m, 16H, Ar-H); Mass spectra: $C_{37}H_{33}N_7O_7$: m/z = 687.2 (100%).

Ethyl (5-(2-hydroxy-3-((3-nitrophenyl)diazenyl) phenyl)-1-methyl-4-(4-methylbenzoyl)-3-oxo-2-phenyl-2,3,4,5-tetrahydro-1H-pyrazolo-pyridin-6-ylamino)acetate (7d): Yellow crystal; Yield 87%; m.p.: 157-158^{o}C; FT-IR (KBr, cm^{-1}): 3098 (N-H), 3069 (-OH), 2850 (-CH_3), 1654 (C=O), 1532 (-NO_2), 1426 (N=N), 1284 (C-N); ^{1}H NMR (400 MHz, DMSO d_6): 2.0 (br, s, 1H, -NH), 5.14 (s, 1H, -OH), 3.65 (s, 2H, -CH_2), 2.47 (s, 3H, -CH_3), 4.12 (q, 2H, -CH_2), 1.36 (t, 3H, -CH_3), 5.56 (s, 1H, -CH), 2.35 (s, 3H, -CH_3), 7.24-8.32 (m, 16H, Ar-H); Mass spectra: $C_{37}H_{33}N_7O_7$: m/z = 687.25 (100%).

Ethyl (4-(2-chlorobenzoyl)-5-(2-hydroxy-3-((3-nitrophenyl)diazenyl)phenyl)-1-methyl-3-oxo-2-phenyl-2,3,4,5-tetrahydro-1H-pyrazolo-pyridin-6-ylamino)acetate (7e): Pale yellow crystal; Yield 82%; m.p.: 155-156^{o}C; FT-IR (KBr, cm^{-1}): 3098 (N-H), 3065 (O-H), 1657 (C=O), 1533 (-NO_2), 1425 (N=N), 1283 (C-N), 781 (C-Cl); ^{1}H NMR (400 MHz, DMSO d_6): 2.0 (br, s, 1H, -NH), 5.12 (s, 1H, -OH), 3.61 (s, 2H, -CH_2), 2.47 (s, 3H, -CH_3), 4.12 (q, 2H, -CH_2), 1.30 (t, 3H, -CH_3), 5.56 (s, 1H, -CH), 7.18-8.39 (m, 16H, Ar-H); Mass spectra: $C_{36}H_{30}ClN_7O_7$: m/z = 707.19 (100%).

Ethyl (4-(4-chlorobenzoyl)-5-(2-hydroxy-3-((3-nitrophenyl)diazenyl) phenyl)-1-methyl-3-oxo-2-phenyl-2,3,4,5-tetrahydro-1H-pyrazolo-pyridin-6-ylamino)acetate (7f): Yellow crystal; Yield 75%; m.p.:150-151^{o}C; FT-IR (KBr, cm^{-1}): 3098 (N-H), 3065 (O-H), 1654 (C=O), 1536 (-NO_2), 1427 (N=N), 1284 (C-N), 783 (C-Cl); ^{1}H NMR (400 MHz, DMSO d_6): 2.0 (br, s, 1H, -NH), 5.14 (s, 1H, -OH), 3.62 (s, 2H, -CH_2), 2.47 (s, 3H, -CH_3), 4.13 (q, 2H, -CH_2), 1.31 (t, 3H, -CH_3), 5.56 (s, 1H, -CH), 6.90-7.89 (m, 16H, Ar-H); Mass spectra: $C_{36}H_{30}ClN_7O_7$: m/z = 708.12 (100%).

Ethyl (5-(2-hydroxy-3-((3-nitrophenyl)diazenyl) phenyl)-4-(2-hydroxybenzoyl)-1-methyl-3-oxo-2-phenyl-2,3,4,5-tetrahydro-1H-pyrazolo-pyridin-6-ylamino)acetate (7g): Pale yellow crystal; Yield 88%; m.p.:174-175^{o}C; FT-IR (KBr, cm^{-1}): 3095 (N-H), 3087 (O-H), 1657 (C=O), 1533 (-NO_2), 1425 (N=N), 1281 (C-N); ^{1}H NMR (400 MHz, DMSO d_6): 2.0 (br, s, 1H, -NH), 5.0 (s, 1H, -OH), 5.12 (s, 1H, -OH), 3.61 (s, 2H, -CH_2), 2.47 (s, 3H, -CH_3), 4.12 (q, 2H, -CH_2), 1.35 (t, 3H, -CH_3), 5.56 (s, 1H, -CH), 6.95-7.78 (m, 16H, Ar-H); Mass spectra: $C_{36}H_{31}N_7O_8$: m/z = 689.22 (100%).

Ethyl (5-(2-hydroxy-3-((3-nitrophenyl)diazenyl) phenyl)-4-(4-hydroxybenzoyl)-1-methyl-3-oxo-2-phenyl-2,3,4,5-tetrahydro-1H-pyrazolo-pyridin-6-ylamino)acetate (7h): Yellow crystal; Yield 85%; m.p.:170-171^{o}C; FT-IR (KBr, cm^{-1}): 3094 (N-H),

3089 (O-H), 1655 (C=O), 1535 (-NO_2), 1425 (N=N), 1283 (C-N); ^{1}H NMR (400 MHz, DMSO d_6): 2.0 (br, s, 1H, -NH), 5.10 (s, 1H, -OH), 5.15 (s, 1H, -OH), 3.64 (s, 2H, -CH_2), 2.47 (s, 3H, -CH_3), 4.18 (q, 2H, -CH_2), 1.36 (t, 3H, -CH_3), 5.56 (s, 1H, -CH), 6.91-7.57 (m, 16H, Ar-H); Mass spectra: $C_{36}H_{31}N_7O_8$: m/z = 689.21 (100%).

***In-vivo* analgesic activity:** The test was carried out using Eddy's hot plate apparatus [20]. Rats of either sex weighing between 150-200 g were used and divided into eight groups of six animals each. The temperature of hot plate was maintained at 55±1^{o}C. Rats were placed on hot plate and recorded the reaction time in second for flicking the hind paw or licking or jumping with cut off time of 15 s. The reaction time following the oral administration of the test compounds (250 mg/kg), reference standard Morphine Sulfate (10 mg/kg) and control saline vehicle were measured at 0, 30, 60, 90 and 120 min.

***In-vivo* anti-inflammatory activity:** Winter *et al*., [21] method was used to induce inflammation by injecting carrageenan in hind paw of Wistar Albino rats. Rats of either sex weighing between 150-200g 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 (250 mg/kg) and reference drug (Diclofenac, 10 mg/kg), freshly prepared 0.1ml carrageenan (1% carrageenan 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 [22].

Paw volume was recorded at the interval of 0, 1, 3 and 5h after carrageenan injection. Results were expressed as an increase in paw volume in comparison to the initial paw volumes and in comparison with control group.

RESULTS AND DISCUSSION: In this study, we report the synthesis of azo dye by diazotization of 3-nitroaniline with sodium nitrite followed by coupling with 2-hydroxy benzaldehyde. This azo dye compound is then condensed in Ugi four component reaction using Zeolite as a catalyst by conventional stirring method. The model reaction **Scheme 1** gave the pure product **7 (a-h)** in 75-92% yield in 6-12h of stirring.

The *in-vivo* analgesic screening results **Table 1** showed significant activity as evidenced by the increase in reaction time to the pain stimulus. Compounds **7a**, **7d**, **7f** and **7h** found to possess excellent analgesic activity when compared with the standard drug Morphine Sulfate. The results were significant at $P < 0.05$ for Eddy's Hot plate method.

In-vivo anti-inflammatory screening results **Table 2** indicate that compounds **7a, 7d, 7g** and **7h** show significant increase in % inhibition of paw oedema. In general, an increase in % inhibition of paw oedema was observed as time interval increases for all the synthesized compounds when compared with the standard drug, Diclofenac.

On the basis of screening data obtained from *in-vivo* studies, we have concluded that the synthesized moieties are equipotent analgesic and anti-inflammatory agents.

TABLE 1 ANALGESIC ACTIVITY OF COMPOUNDS 7 (a-h) by EDDY'S HOT PLATE METHOD

Test compounds (250 mg/kg)	Response time (min)[a]				
	0	**30**	**60**	**90**	**120**
Control	2.33 ± 0.2	2.30 ± 0.3	2.34 ± 0.3	2.28 ± 0.1	2.35 ± 0.2
7a	3.12 ± 0.4	5.15 ± 0.3	7.10 ± 0.3**	9.18 ± 0.1**	11.21± 0.4
7b	2.11 ± 0.3	3.83 ± 0.1**	4.33 ± 0.2	6.75 ± 0.7	8.60 ± 0.2**
7c	2.22 ± 0.5	4.72 ± 0.2**	6.13 ± 0.3	8.20 ± 0.5	9.41 ± 0.3
7d	3.31 ± 0.2	6.14 ± 0.4	8.12 ±0.4	10.20 ± 0.1**	12.15 ± 0.4
7e	3.02 ± 0.4	5.01 ± 0.2	5.26 ± 0.1**	8.10 ±0.2	9.52 ± 0.2**
7f	3.11 ± 0.2**	6.09 ± 0.2**	8.16 ± 0.3	10.32 ± 0.3	12.45 ± 0.5
7g	2.81 ± 0.3	5.07 ± 0.3	6.16 ± 0.1**	8.11 ± 0.7	9.81 ± 0.2
7h	3.81 ± 0.2	7.09 ± 0.3	7.16 ± 0.3	10.22 ± 0.2	12.10 ± 0.2**
Morphine Sulfate (10 mg/kg)	7.4 ± 0.3**	9.62 ± 0.4	10.82 ± 0.1**	11.52 ± 0.2**	14.21 ± 0.3**

*Significantly different from control at $P < 0.05$. [a] Results are expressed as mean ± SEM and compared with student "t" test.

TABLE 2 ANTI-INFLAMMATORY ACTIVITY OF COMPOUNDS 7 (a-h) USING CARRAGEENAN INDUCED PAW OEDEMA IN RATS

Test Compounds	% Inhibition of paw oedema at different time (h) interval [a]			
	250 mg/kg			
	0	1	3	5
Control [b]	1.34 ± 0.15 (0.0)	1.41 ± 0.1 (0.0)	1.48 ± 0.2 (0.0)	1.45 ± 0.3 (0.0)
7a	1.15 ± 0.03 (33.78)	1.17 ± 0.12 (30.81)	1.21 ± 0.15 (65.53)	1.19 ± 0.03* (70.12)
7b	1.22 ± 0.13 (20.16)	1.25 ± 0.12* (15.02)	1.28 ± 0.21 (40.11)	1.26 ± 0.03 (55.31)
7c	1.31 ± 0.01* (15.71)	1.33 ± 0.03 (28.25)	1.37 ± 0.05 (34.16)	1.33 ± 0.02* (42.11)
7d	1.16 ± 0.08 (30.52)	1.19 ± 0.06 (55.46)	1.22 ± 0.13* (64.32)	1.20 ± 0.08 (71.24)
7e	1.33 ± 0.14 (11.05)	1.36 ± 0.05 (22.17)	1.41 ± 0.12* (38.25)	1.37 ± 0.07 (54.10)
7f	1.12 ± 0.05* (35.06)	1.13 ± 0.14 (38.13)	1.18 ± 0.03 (64.14)	1.14 ± 0.05 (67.03)
7g	1.14 ± 0.06 (20.19)	1.33 ± 0.04 (36.12)	1.36 ± 0.17 (57.02)	1.34 ± 0.06* (70.24)
7h	1.12 ± 0.16 (33.14)	1.14 ± 0.04 (53.13)	1.15 ± 0.06 (67.01)	1.13 ± 0.12* (72.53)
Diclofenac (10 mg/kg)	1.04 ± 0.03* (71.33)	1.08 ± 0.01* (74.24)	1.16 ± 0.02* (78.12)	1.15 ± 0.03* (80.65)

*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

CONCLUSION: In this paper, we have studied in-vivo analgesic and anti-inflammatory activities of the synthesized novel compounds from Ugi-4CR using Zeolite as catalyst. Higher yields were achieved within a framework of green chemistry protocol. This study reveals that the synthesized compounds are potent analgesic and anti-inflammatory agents when compared with the standard reference drugs respectively. Moreover, reusability, low cost, and ease of isolation are the remarkable features of the catalyst.

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