SYNTHESIS AND EVALUATION OF SOME NOVEL [3-ISONICOTINOYL-5-(4-SUBSTITUTED)-2, 3-DIHYDRO-1, 3, 4-OXADIAZOL-2-YL] DERIVATIVES FOR ANTI-INFLAMMATORY ACTIVITY

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Summary

A series of [3-isonicotinoyl-5-(4-substituted)-2, 3-dihydro-1, 3, 4-oxadiazol-2-yl] derivatives has been synthesized and evaluated for their anti- inflammatory activity using Carragenan induced Rat paw edema method. The newly synthesized compounds have been characterized by IR, ^{1}H NMR and CHN analysis. All the compounds have shown promising anti-inflammatory activity when compared with standard drug Diclofenac.

Keywords: [3-isonicotinoyl-5-(4-substituted)-2, 3-dihydro-1,3,4-oxadiazol-2-yl], Anti-inflammatory activity.

Introduction

The subject of drugs is as old as disease. Illness has been man's heritage from the beginning of his existence, and the search for remedies combat it is perhaps equally old. The sincere attempt by man to control and cure diseases has led to the search of new drugs or suitable derivatives of existing drugs. The earlier sources of drugs were from plant, animal and mineral sources, but due to the lack of potential action and definitive cure and sometimes more toxicity, the discovery of new drugs that are more potential and less toxic is essential. The synthesis of derivatives has been an important part and is aimed at modifying the action of drugs, particularly to reduce the side effects and to potentiate the drug action. Today more than 60% of drugs were used in practice are synthesized derivatives and day-by-day the scope of synthetic medicinal chemistry is broadening.

The discipline of medicinal chemist is devoted to the discovery and development of new agents for treating diseases. Most of this activity is directed to natural or synthetic organic compounds. Inorganic compounds continue to be important in therapy, e. g. trace elements in nutrition therapy, antacids and radiopharmaceuticals, but organic molecules with increasingly specific pharmacological activities are clearly dominant. Development of organic compounds has grown beyond traditional synthetic methods.

The process of establishing new pharmaceuticals is exceeding complex and involves the talents of the people from a variety of disciplines including chemistry, biochemistry, molecular biology, physiology, pharmacology, pharmaceutics and medicine. Medicinal chemistry itself is concerned mainly with organic, analytical and biochemical aspects of this process, but the chemist must interact productively with those in other disciplines. Thus medicinal chemist occupies a strategic position at the interface of chemistry and biology.

Thousands of new organic chemicals were synthesized annually throughout the world and hundreds of them are entered into pharmacological screens to determine whether they have useful biological activity. Only few of them were come to the clinical trials. This process of random screening has been considered insufficient, but it has resulted in the identification of new lead compounds whose structures have been optimized to produce clinical agents. Sometimes, lead develops by careful observation of the pharmacological behavior of the existing drug. [1]

Now a day's medicinal chemists are at the forefront of innovation, blending synthetic chemistry, molecular modeling, computational biology, structural genomics and

pharmacology to discovery and design new drugs and investigate their interaction at the cellular level. Many efforts are being made in the design and development of novel drugs from synthetic origin. Thus there is growing interest in the pharmacological potential.

From the review of literature it is known that substituted 5-aryl 1, 3, 4-oxadiazole have been reported for number of biological activity.[4,5] Based on these observations it was planned to synthesize some 5-aryl-1, 3, 4-oxadiazole derivatives and screened for anti-inflammatory activity.

Result and Discussion

The compounds were synthesized as per **Scheme** 5-aryl-1,3,4-oxadiazole derivatives were synthesized by reacting Isoniazid with substituted aldehydes to give Schiff's base which on further reaction with aromatic acids in presence of phosphorousoxychloride gives corresponding 5-aryl-1,3,4-oxadiazole derivatives. The structures of the synthesized compounds were confirmed by IR, NMR and CHN analysis. All these compounds were screened for anti- inflammatory activity using standard method in well equipped pharmacology laboratory. Compounds **1b, 2a, 2c,** and **3c** have shown promising anti-inflammatory activity when compared with standard drug Diclofenac.

Methodology for studying anti- inflammatory activity

Carrageenan Induced Rat hind Paw Edema: [1,2]

Anti-inflammatory activity was determined by Carrageenan Induced Rat hind Paw method of winter et al. wistar rats (120-150 g) was used for the experiment. The conventional laboratory diet was fed with adequate supply of drinking water. The animals were randomly selected, marked to permit individual identification and kept in polypropylene cages for one week prior to dosing to allow acclimatization of them to laboratory conditions. The drugs were prepared as a suspension by triturating with water and 0.5% sodium CMC. The standard group received 50mg/kg body weight of Diclofenac Sodium, test group received 200mg/kg body weight of synthesized compounds and the control group received 1% w/v of CMC.

Experimental

Melting points were determined in open capillary method and are uncorrected. Purity of the compound was checked on Silica gel TLC plates. IR spectra were recorded on Thermo Nicolate IR 200 spectrophotometer using KBr disc method. ^{1}H NMR spectra were recorded on Bruker AMX-400, $CDCl_3$ as solvent and TMS as internal standard. Combustion analyses were found to be within the limits of permissible errors.

SCHEME

Synthesis of N'-(substituted) isonicotinohydrazide (1-3).[4]

To a mixture of 0.05 mole of Isoniazid in 18 ml of water and 2.4 ml of concentrated ammonia. 0.05 mole of anisaldehyde was added dropwise with stirring over a period of 30-60 minutes. The mixture was stirred for further hour, the solid was collected by suction filtration washed with water and recrystallized from ethanol to give 1. Similarly 2 and 3 were prepared using p-chlorobenzaldehyde and Furfuraldehyde. Analytical data were given in the table.

Synthesis of [3-isonicotinoyl-5-(4-substituted)-2, 3-dihydro-1, 3, 4-oxadiazol-2-yl] (1a-3c) [5]

To a mixture of 0.01 mole of $\mathbf{I_1}$ and 0.01 mole of Mefenamic acid was added 10 mole of Phosphorus oxychloride at temp. of -5^{0}c. The reaction mixture refluxed at 100 ^{0} C for 2 hrs.The reaction mixture was cooled to room temperature, the excess of $POCl_3$ was concentrated through high vacuum, the residue was quenched with ice and the solid separated was filtered and dried through pump to afford corresponding aryl Oxadiazole (**1a**). Similarly **1b-3c** was prepared using **2** and **3** along with **Para Amino Benzoic acid and Salicylic acid** respectively.

Spectral Data:

SCHEME

1a: IR Bands (cm^{-1}): 3254 .68,-NH str.; 3010.23 ,Ar-CH str., 2827.36 ,Alkyl CH str.; 1678.36 ,-C=O str.; 1525.32 ,-C=N str.; 1245.36 ,-C-N str.; 1016.38 ,-C-O-C str. **^{1}H NMR (δ ppm):** 8.1-8.6 , 4H of pyridine; 6.8-7.2 , 8H of phenyl; 6.4-6.8, 1H of 1, 3, 4-oxadiazole; 2.2-2.4 2H of NH_2; 1.2-1.6 3H of CH_3.

1b : IR Bands (cm^{-1}): 3344.68, -O-H str.; 2947.33,Ar-CH str., 2831.60,Alkyl CH str.; 1662.69,-C=O str.; 1508.38,-C=N str.; 1249.91,-C-N str.; 1026.16,-C-O-C str.

^{1}H NMR (δ ppm): 8.2-8.6 , 4H of pyridine; 6.7-7.1 , 8H of phenyl; 6.2-6.6, 1H of 1, 3, 4-oxadiazole;5.2-5.4 1H of OH; 1.3-1.53H of CH_3.

1c : IR Bands (cm^{-1}): 3290.67, -NH str.; 3132.50,Ar-CH str.; 2831.60,Alkyl CH str.; 1684.56 ,-C=O str.; 1523.88 ,-C=N str. 1246.06 ;-C-N str.; 1010.73,-C-O-C str. **^{1}H NMR (δ ppm):** 8.3-8.5, 4H of pyridine; 6.5-6.7, 11H of phenyl; 6.2-6.6, 1H of 1, 3, 4-oxadiazole;5.2-5.4 1H of OH; 2.3-2.5 1H of NH; 1.4-1.6 9H of CH_3.

2 a : IR Bands (cm^{-1}): 3245.38 NH str.; 3085 .07,Ar-CH str.; 1666.41,-C=O str.; 1572.64 ,-C=N str.; 1236.24 ,-C-N str.; 1015.37 ,-C-O-C str. **^{1}H NMR (δ ppm):** 7.8-8.2

, 4H of pyridine; 7.0.7.2, 8H of phenyl; 6.4-6.7, 1H of 1, 3, 4-oxadiazole; 2.1-2.4 2H of NH_2.

2b : IR Bands (cm^{-1}): 3267.52-O-H str.; 3144.07,Ar-CH str.; 1670.41,-C=O str.; 1612.54,-C=N str.; 1246.06,-C-N str.; 1030.06,-C-O-C str. **^{1}H NMR (δ ppm):** 8.0-9.0 , 4H of pyridine; 7.2-7.6, 8H of phenyl; 6.6-6.8, 1H of 1, 3, 4-Oxadiazole; 5.0,1 H of –OH.

2c : IR Bands (cm^{-1}): 3302.24, -NH str.; 2947.33, Ar-CH str.; 2835.45, Alkyl CH str.; 1654.98, -C=O str.; 1570.11, -C=N str.; 1235.77, -C-N str.; 1026.16, -C-O-C str. **^{1}H NMR (δ ppm):** 8.0-8.2, 4H of pyridine; 6.4-6.8, 11H of phenyl; 6.0-6.2, 1H of 1, 3, 4-Oxadiazole; 2.2-2.4 1H of NH; 1.4-1.6 6H of CH_3.

3a : IR Bands (cm^{-1}): 3244.27 ,-NH str.; 3026.37 ,Ar-CH str.; 1674.24 ,-C=O str.; 1548.17 , -C=N str.; 1210.34 ,-C-N str.; 1014.37 , -C-O-C str. **^{1}H NMR (δ ppm):** 8.0-9.0, 4H of pyridine; 6.4-6.8, 4H of phenyl; 6.2.-6.4, 3H of furan; 6.0, 1H of oxadiazole; 3.8-4.2, 2H of NH_2.

3b : IR Bands (cm^{-1}): 3286.81,-O-H str.; 3056.89,Ar-CH str.; 1670.41,-C=O str.; 1608.69, -C=N str.; 1114.89,-C-N str.; 1026.16, -C-O-C str. **^{1}H NMR (δ ppm):** 7.8-8.2, 4H of pyridine; 6.6-7.0, 4H of phenyl; 6.0-6.3, 3H of furan; 6.4-6.8, 1H of oxadiazole; 5.2-5.6 1H of –OH.

3c : IR Bands (cm^{-1}): 3356.25, -NH str.; 3067.65, Ar-CH str.; 2840.32, Alkyl CH str.; 1662.69,-C=O str.; 1454.38, , -C=N str.; 1296.21, ,-C-N str.; 1030.02,-C-O-C str. **^{1}H NMR (δ ppm):** 8.2-8.6, 4H of Pyridine; 6.4-6.8, 7H of phenyl; 6.0-6.4, 3H of furan; 5.8-6.4 , 1H of oxadiazole; 2.8-3.2, 1H of NH; 1.2-1.6 6H of CH_3.

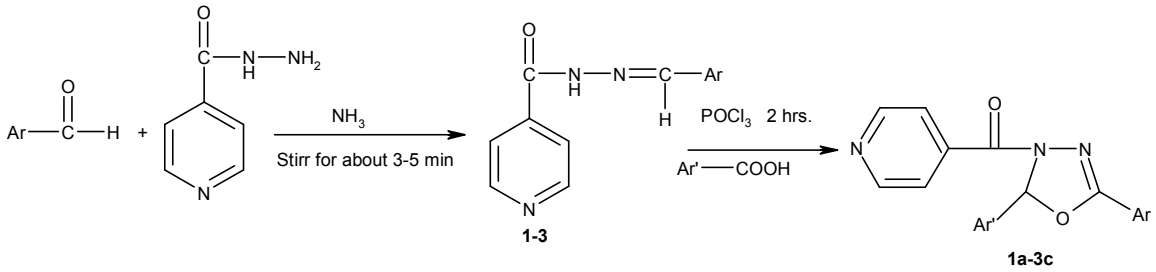
Table No. 1 : Analytical data of [3-isonicotinoyl-5-(4-substituted)-2, 3-dihydro-1,3,4-oxadiazol-2-yl] compounds (scheme).

Comp.	Mol. Formula	Mol. Wt.	M.P ^{0}C	Rf Value	Yield %	Elemental analyses Calcd. (Found)			LogP	CLogP	CMR
						C	H	N			
1a	$C_{21}H_{18}N_4O_3$	374.39	233-235	0.63	63	67.37	4.85	14.96	3.34	1.87	10.75
1b	$C_{21}H_{17}N_3O_4$	375.37	158-160	0.52	44	67.19 (66.95)	4.56 (4.26)	11.19 (10.86)	3.75	2.38	10.53
1c	$C_{29}H_{26}N_4O_3$	478.54	140-142	0.59	58	72.79	5.48	11.71	6.58	5.47	14.19
2a	$C_{20}H_{15}ClN_4O_2$	378.81	138-140	0.51	38	63.41 (63.18)	3.99 (3.80)	14.79 (14.56)	4.02	2.66	10.62
2b	$C_{20}H_{14}ClN_3O_3$	379.79	148-150	0.52	45	63.25	3.72	11.06	4.44	3.17	10.41
2c	$C_{28}H_{23}ClN_4O_2$	482.96	152-154	0.56	52	69.63	4.80	11.60	7.27	6.26	14.06
3a	$C_{18}H_{14}N_4O_3$	334.32	162-163	0.54	46	64.66	4.22	16.46	2.08	1.12	9.34

3b	$C_{18}H_{13}N_3O_4$	335.31	174-176	0.51	58	64.67	3.91	12.53	2.49	1.68	9.13
3c	$C_{26}H_{22}N_4O_3$	438.47	125-127	0.53	54	71.22	5.06	12.78	5.32	4.73	12.78

The combustion analyses of compounds synthesized were found to be within the limits of (±0.4).

SCHEME



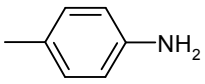
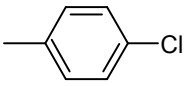
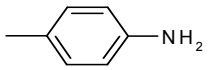
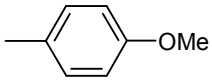
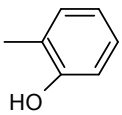
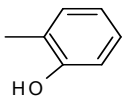
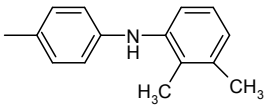
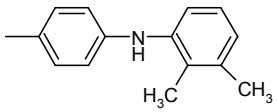
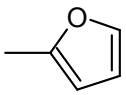
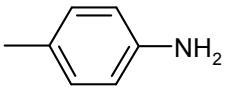
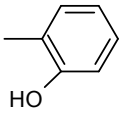
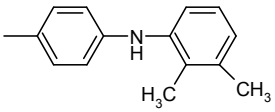
Comp	Ar	R	Comp.	Ar	R
1a			**2a**		
1b			**2b**		
1c			**2c**		
3a					
3b					
3c					

Table No. 2: Anti-inflammatory activity of [3-isonicotinoyl-5-(4-substituted)-2, 3-dihydro-1, 3, 4-oxadiazol-2-yl] compounds:

Comp	Mean paw oedema volume ± SE					% inhibition at 4th hr
	0 hour	1 hour	2 hour	3 hour	4 hour	
Ct.	0.975±0.025	1.475±0.025	1.650±0.028	1.775±0.025	1.842±0.012	
Std.	0.975±0.025	1.225±0.025**	1.325±0.025**	1.350±0.028**	1.275±0.025**	**44.47**
1a	1.10±0.040	1.225±0.025**	1.480±0.040*	1.575±0.025**	1.625±0.025**	13.35
1b	**1.000±0.021**	**1.350±0.028**	**1.425±0.045****	**1.500±0.040****	**1.425±0.047****	**29.26**
1c	1.040±0.041	1.400±0.042	1.575±0.025ns	1.600±0.0**	1.635±0.025*	12.266
2a	**1.060±0.0**	**1.375±0.025**	**1.435±0.028****	**1.440±0.025****	**1.320±0.040****	**39.54**
2b	0.975±0.025	1.350±0.028	1.575±0.025ns	1.575±0.025**	1.675±0.028*	9.97
2c	**0.975±0.025**	**1.400±0.041**	**1.490±0.025***	**1.420±0.025****	**1.364±0.028****	**35.04**
3a	0.950±0.028	1.350±0.029	1.475±0.025**	1.500±0.040**	1.402±0.028**	14.40
3b	0.975±0.025	1.350±0.028	1.500±0.040*	1.600±0.0**	1.370±0.025*	15.84
3c	**0.975±0.025**	**1.375±0.047**	**1.475±0.047****	**1.610±0.120***	**1.575±0.025***	**16.95**

One way ANOYA followed by Dunnett's 't' test **P<0.01

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