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Design and Microwave-assisted Synthesis of 1,3,4-Oxadiazole Derivatives for Analgesic and Anti-inflammatory Activity

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ABSTRACT

1,3,4-Oxadizoles form a biologically important group of compounds having activities like analgesic, anti-inflammatory, bactericidal, antifungal, anticonvulsant, psychotropic, plant growth regulating and mono amino oxidase inhibition. This research has focused on the incorporation of the oxadiazole moiety into isoniazid because of their versatile biological action, to get 2-aryl-5-(4-pyridyl)-1,3,4-oxadiazole to explore the possibilities of some altered biological action. 1,3,4-Oxadiazole derivatives were synthesized by microwave-assisted synthesis and screened for their analgesic, anti-inflammatory activities. The synthesized compounds were characterized by Melting point, Thin layer chromatographyInfra red, Nuclear magnetic resonance spectroscopy, etc. Almost all the synthesized compounds possessed good activity as compared to the standard.

Key words: 1,3,4-Oxadiazole, analgesic, anti-inflammatory, isoniazid

INTRODUCTION

Microwave-enhanced synthesis[1,2] represents a fundamental step forward in the capabilities of synthetic chemistry. It allows organic chemists to work faster, generating higher yields with increased product purity, and to scale experiments up reliably from milligrams to much larger quantities without the need to alter reaction parameters. It offers much more precise control over conditions of temperature and pressure than any previous technology. Ultimately, by eliminating much of the time and effort from the process of performing chemical reactions, it allows chemists to focus on what is most important—the development of new compounds, or refined methods for generating known products. In a solvent-less reaction all the microwave energy is directly absorbed by the reactant molecules.[3] Under these conditions, the non-thermal microwave effect will be operative at high efficiency.

This work aims at the development of a newer isoniazid-based oxadiazole ring system. 1,3,4-Oxadiazole derivatives show a broad spectrum of biological activities, which include analgesic and anti-inflammatory, antimicrobial, anticonvulsant, antifungal, anticancer,

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antimycobacterial,[3,4] etc. The research envisages a meaningful exploration of this lead molecule for novel analgesic, anti-inflammatory activities with minimum toxicity and high potency.[5] The lead compound was structurally modified by incorporating various substitutions at the second and fifth position of the heterocyclic ring system [Table 1]. From a review of the literature it is clear that 2,5 disubstituted 1,3,4-oxadiazole derivatives of oxadiazole possess remarkable analgesic, anti-inflammatory activity.[5,6]

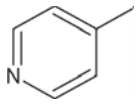
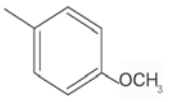
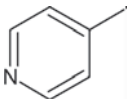
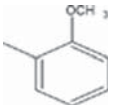
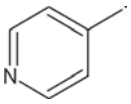
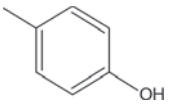
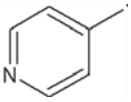
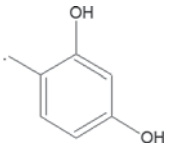
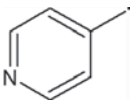
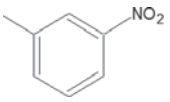
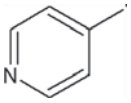
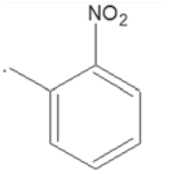
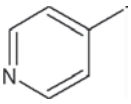
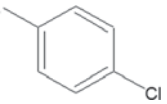
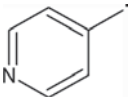
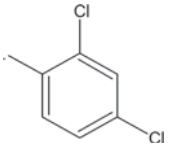
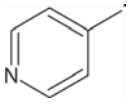
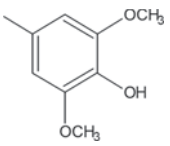
MATERIALS AND METHODS

Microwave-assisted synthetic procedure

Step 1

A mixture of (0.01 mole, 1.37 g) isoniazid, (0.01 mole) aromatic aldehyde and DMF (5 drops) was subjected to microwave irradiation at 300 w internally at 30-sec intervals for 3 min. The reaction mixture was cooled and treated with ice cold water. The resulting solid product was

Table 1: SMILES and cLog *P* values of proposed analogues (generated by *molinspiration* software)

Compound	R_1	R_2	SMILES notation	cLog *P*
2a			COc3ccc(c2nnc(c1ccncc1)o2)cc3	2.494
2b			COc1ccccc1c3nnc(c2ccncc2)o3	2.446
2c			Oc3ccc(c2nnc(c1ccncc1)o2)cc3	1.958
2d			Oc3ccc(c2nnc(c1ccncc1)o2)c(O)c3	1.667
2e			O = N(= O)c3cccc(c2nnc(c1ccncc1)o2)c3	2.372
2f			O = N(= O)c1ccccc1c3nnc(c2ccncc2)o3	2.348
2g			Clc3ccc(c2nnc(c1ccncc1)o2)cc3	3.115
2h			Clc3ccc(c2nnc(c1ccncc1)o2)c(Cl)c3	3.721
2i			COc3cc(c2nnc(c1ccncc1)o2)cc(OC)c3O	1.792

filtered, washed with water and recrystallized from ethanol [Table 2].[7-11]

Step 2

To a solution of compound 1a (0.01 mole) in ethanol (15 ml), chloramine-T (0.01 mole) was added. The reaction mixture was exposed to microwave irradiation at 300W internally at 30-sec intervals for 4 min. The reaction mixture was cooled and digested with cold water. The solid thus obtained was filtered, washed with water and recrystallized from methanol to give the product [Figure 1].[9,11-13]

RESULTS AND DISCUSSION

The purity of the synthesized molecules was ascertained routinely by TLC, and melting points were noted with an open capillary tube method and are uncorrected.[12-16]

Infra-red spectral analysis

Infra-red (IR) spectra were recorded using KBr pellets in the range of 4000-500 cm^{-1} on Jasco FTIR model 4100 type A to elucidate the structure of the compounds [Table 3].

^{1}H NMR spectral analysis

Proton NMR (300 MHz) spectra were recorded in $CDCl_3$. Chemical shifts were recorded in parts per million downfield with reference to internal standard Tetra Methyl Silane (TMS) on BurkerAvance DPX 300. The total number of proton obtained from NMR spectra was in accordance with that of respective analogues.

PHARMACOLOGICAL SCREENING

Acute toxicity study

A prototype molecule was randomly selected for the study of the safety dose range of the analogues.[11,14,15]

Table 2: Characteristic ^{1}H NMR spectrum of the synthesized compounds

Compound	^{1}H NMR ($CDCl_3$) δ ppm
2a	^{1}HNMR ($CDCl_3$) δ ppm: 2.54(1H, O-H), 6.13-7.78(Ar-H, 8H)
2b	^{1}HNMR ($CDCl_3$) δ ppm: 2.52(1H, O-H), 4.23-7.9(Ar-H, 8H)
2c	^{1}HNMR ($CDCl_3$) δ ppm: 2.40(1H, O-H), 7.23-7.78(Ar-H, 8H)
2d	^{1}HNMR ($CDCl_3$) δ ppm: 2.40(2H, O-H), 6.22-7.78(Ar-H, 8H)
2e	^{1}HNMR ($CDCl_3$) δ ppm: 2.85(2H, O-H), 7.23-6.98(Ar-H, 8H)
2f	^{1}HNMR ($CDCl_3$) δ ppm: 2.40(1H, O-H), 8.23-7.88(Ar-H, 8H)

Table 3: Characteristic IR peaks of the synthesized compounds

Compound	IR (KBr vcm^{-1})
2a	3240.79(Methyl C-H stretching),1597.739(C-H bend, alkyl),1326.79(C-N(stretching(ring)),1151.29 (Phenolic C-Ostretch),1085.73(Symmetric C-O-C ring stretch),670.14(aromatic bend)
2b	3340.79(N-H stretching),1597.739(C-H bend, alkyl),1326.79(C-N stretching(ring)),1151.29 (Phenolic C-Ostretch),1085.73(Symmetric C-O-C ring stretch),670.14(aromatic bend)
2c	3322.39(OH(Phenolic)stretching),1573.63(C=C (aromatic)stretching),1495.53(OHbending),1325.82 (CN(stretching(ring)),1172.51(asymmetric C-O-C ring stretch)670.14(C-H aromatic bend)
2d	3322.39(OH(Phenolic)stretching),1573.63(C=C (aromatic)stretching),1495.53(OHbending),1325.82 (CN(stretching(ring)),1172.51(asymmetric C-O-C ring stretch)670.14(C-H aromatic bend)
2e	3434.6(AromaticCHstretch),1529.27 (asymmetric($ArNO_2$)(N=O)stretch),1411.64(C Nstretching(ring)),1299.79(symmetric($ArNO_2$) (N=O)stretch),1155.15(asymmetric C-O-C ring stretch)814.77(C-N stretch($ArNO_2$))
2f	3434.60(AromaticCHstretch),1303.64(symmetric ($ArNO_2$)(N=O)stretch),1159.01(asymmetric C-O-C ring stretch)
2g	3019,(C-H str), 1590.02,(C=N imine stretching)1260(C-O str),820(C-Haromatic bending),614.21(C-Cl stretching)
2h	3019,(C-H str),1590.02,(C=N imine stretching),1260(C-O str),820(C-Haromatic bending),614.21(C-Cl stretching)
2i	3359.39 (O-H stretching), 3261.04 (Methyl C-H stretch), 1495.53 (O-H bending), 1389.46 (Alkyl C-H bend), 1159.01 (Phenolic C-O stretch), 1097.3 (Symmetric C-O-C (ring) stretch).669.17(C-H bend)

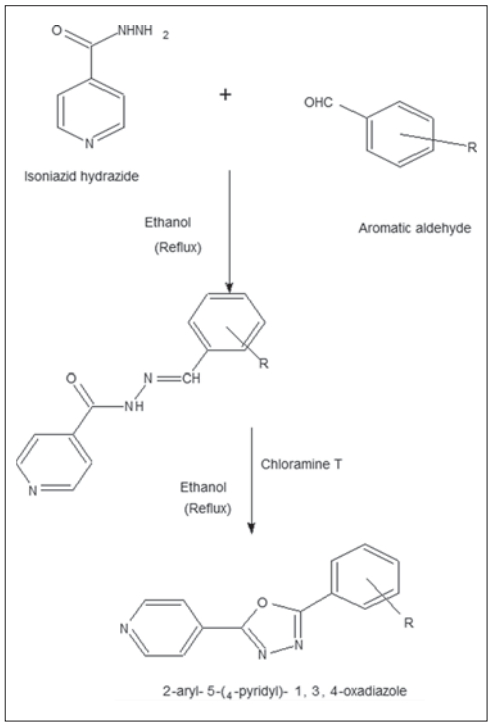
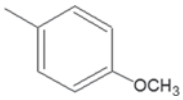
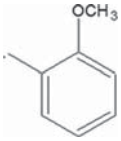
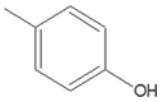
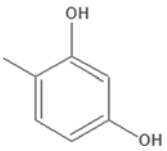
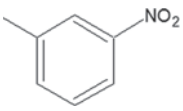
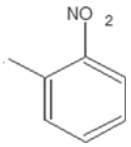
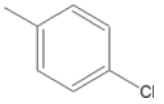
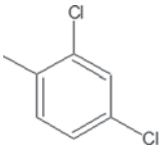
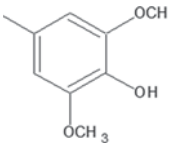


Figure 1: Synthetic scheme of 1,3,4 oxadiazole derivative

Table 4: Physicochemical properties of the proposed analogues (generated by *ACDLABS* software)

Compound	Molar refractivity cm^3	Molar volume cm^3	Parachor cm^3	Polarizability cm^3	cLog *P*
2a	68.68 ± 0.3	206.4 ± 3.0	547.0 ± 4.0	27.23 ± 0.5 10^{-24}	2.494
2b	68.68 ± 0.3	206.4 ± 3.0	547.0 ± 4.0	27.23 ± 0.5 10^{-24}	2.446
2c	63.89 ± 0.3	180.8 ± 3.0	505.4 ± 4.0	25.32 ± 0.5 10^{-24}	1.958
2d	65.77 ± 0.3	179.3 ± 3.0	520.4 ± 4.0	26.07 ± 0.5 10^{-24}	1.667
2e	68.55 ± 0.3	194.3 ± 3.0	545.8 ± 4.0	27.17 ± 0.5 10^{-24}	2.372
2f	68.55 ± 0.3	194.3 ± 3.0	545.8 ± 4.0	27.17 ± 0.5 10^{-24}	2.348
2g	66.90 ± 0.3	194.4 ± 3.0	526.2 ± 4.0	26.52 ± 0.5 10^{-24}	3.115
2h	71.80 ± 0.3	206.3 ± 3.0	562.1 ± 4.0	28.46 ± 0.5 10^{-24}	3.721
2i	77.24 ± 0.3	228.9 ± 3.0	= 618.7 ± 4.0	30.62 ± 0.5 10^{-24}	1.792

Table 5: Physicochemical data of newly synthesized compounds

Compound	Substituent	Molecular formula	Molecular weight	mp°C	R_f
2a		$C_{14}H_{11}N_3O_2$	253.261	163	0.57
2b		$C_{14}H_{11}N_3O_2$	253.261	165	0.74
2c		$C_{13}H_9N_3O_2$	239.234	159	0.61
2d		$C_{13}H_9N_3O_3$	255.233	160	0.53
2e		$C_{13}H_8N_4O_3$	268.232	160	0.57
2f		$C_{13}H_8N_4O_3$	268.232	168	0.55
2g		$C_{13}H_8ClN_3O$	257.68	163	0.63
2h		$C_{13}H_7Cl_2N_3O$	292.125	163	0.67
2i		$C_{15}H_{13}N_3O_4$	299.286	164	0.52

In this study, it was found that up to 1600 mg/kg dose, the compound is safe. i.e. there was no mortality or gross behavioral change in the animals used.[17-24]

Table 6: Analgesic activity (acetic acid-induced Writhing method)

Name of group	Treatment	No. of Writhing in 20 min (mean+SEM)	Percentage reduction of Writhing
Vehicle control (1%CMC)	20 mg/kg	39.2 ± 0.04	-
Aspirin	40 mg/kg	16.4 ± 0.08	58.16
2a	500 mg/kg	13.6 ± 0.74	65.30
2c	500 mg/kg	12.8 ± 0.48	67.34
2e	500 mg/kg	19.9 ± 0.74	49.23
2g	500 mg/kg	19.4 ± 0.87	50.51
2l	500 mg/kg	16.2 ± 0.73	58.86

Table 7: Anti-inflammatory activity (Carageenan-induced rat paw edema method)

Treatment	Dose (per Kg)	Mean difference in paw thickness = SEM	Percentage inhibition of edema
Vehicle control (1%CMC)	20 mg/kg	2.23 ± 0.09	-
Indomethacin	20 mg/kg	0.72 ± 0.08	67.71
2a	500 mg/kg	0.70 ± 0.03	68.60
2c	500 mg/kg	0.69 ± 0.04	69.05
2e	500 mg/kg	0.96 ± 0.03	56.95
2g	500 mg/kg	0.89 ± 0.02	60.08
2l	500 mg/kg	0.86 ± 0.04	61.43

SUMMARY AND CONCLUSION

This research work was focused on the rational approach in the design and development of 1,3,4 oxadiazole derivatives as novel analgesic, anti-inflammatory drugs.

The candidates which obeyed the Lipinski rule of five were taken for wet lab synthesis. Nine different analogues were synthesized by microwave methods and the purity of the compounds thus synthesized was ascertained by consistency in melting point and Rf value and characterized by UV, IR and ^{1}H NMR spectral studies [Tables 4 and 5].

Among the newly synthesized 1,3,4 oxadiazole analogues

five were screened for analgesic and anti-inflammatory activity and the compounds 2a, 2c and 2i showed good analgesic and anti-inflammatory activity. Acute toxicity studies showed that the analogues were safe with low toxicity. So these derivatives may be future leads for analgesic and anti-inflammatory drug discovery [Tables 6 and 7].

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