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Synthesis and Antimicrobial Activity of Some New 1,2,4-Triazoles

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A variety of 1,2,4-triazole derivatives were synthesized by esterifying substituted aryl carboxylic acid separately. It was then treated with hydrazine hydrate to yield corresponding aromatic acid hydrazides. When these hydrazides were treated with KOH and CS_2, oxadiazoles were obtained. Thus obtained oxadiazoles on further treatment with different acid hydrazides afforded three different series of 1,2,4-triazole derivatives. All the newly synthesized compounds were screened for their antimicrobial activities and 1,2,4-triazoles of anthranilic acid series were found to be very active than the other two series of compounds.

Literature revealed that 1,2,4-triazoles[1,2] showed significant antimicrobial activities and their derivatives[3,4] were also known for their interesting antitubercular and pharmacological activities. This observation and our interest in the synthesis of biologically active heterocyclic compounds encouraged us to synthesis 1,2,4 -triazoles from aryl substituted carboxylic acid by using different acid hydrazides such as hydrazine hydrate, vitamin. nicotinamide and the antitubercular agents isoniazid, pyrazinamide and ethionamide to give antimicrobial activities in triazole form.

The three different triazole series 4A a-e, 4B a-e and 4C a-e were conveniently synthesized by acid esterification of substituted aryl carboxylic acid with ethanol/concentrated Hcl to yield 1A, 1B and 1C which upon refluxing with hydrazine hydrate yield corresponding aromatic acid hydrazides 2A, 2B and 2C. These acid hydrazides 2A, 2B and 2C on treatment with KOH and CS_2 yielded corresponding 3A, 3B and 3C oxadiazoles The title compounds 1,2,4-triazoles were prepared by refluxing oxadiazoles of 3A, 3B and 3C with different acid hydrazides as shown in the scheme. All the newly synthesized compounds were screened for their antibacterial activity against *Staphylococcus aureus* and *Escherichia coli*; and antifungal activity against *Candida albicans* using Kirby Bauer method.

Melting points were determined in open capillary tubes and are uncorrected. Precoated TLC plates were used to check the purity of the compounds. IR spectra were recorded using KBr pellets on a Jasco IR Spectrometer and ^1H NMR spectra were recorded on a Bruker AC 300 MHz FTNMR using TMS as internal standard and chemical shifts were expressed in δ ppm. Elemental analysis was carried out using a Perkin Elmer –2400 CHN analyzer. The compounds 1A, 1B and 1C, 2A, 2B and 2C, 3A, 3B and 3C were pre-

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pared by the procedures given in the literature[5,6].

Oxadiazoles of 3A, 3B and 3C (0.0025 mol each) were made into a suspension with 0.0025 mol of hydrazine hydrate or in any acid hydrazide and refluxed for 4 h. It was then cooled and poured on crushed ice. The solid that separated out was filtered, washed with water, dried and recrystallized from methanol. IR (KBr) spectra of the compounds 4a-e exhibited bands at 3425-3440 (NH), 3089-3160 (ArCH), 1674-1680 (C=N) and 1376-1380 (C=S), ^{1}H NMR ($CDCl_3$) spectrum of the compounds 4a-e displayed signals at δ 6.2 (NH_2), 7.5-8.5 (Ar H) and 9.5 (SH).

All the newly synthesized compounds (at a disc concentration of 100, 200 and 500 μg/ml) were screened for antibacterial activity *in vitro* against Gram positive bacterium *Staphylococcus auerus* and Gram negative bacterium *Eschericha coli* using ofloxacin 10 μg/ml as a standard. For *in vitro* antifungal screening, *Candida albicans* was used with clotrimazole as a standard and DMF was used as control. The culture media was nutrient agar and the method employed was Kirby Bauer method[7,8]. The zones of inhibition formed were measured in mm.

All the p-amino benzoic acid triazoles were highly active against both the organisms of bacteria and fungi only at a disc concentration of 500 μg/ml; none of them were active at 200 and 100 μg/ml disc concentrations. Among the salicylic acid triazole compounds 4B c was weakly active against *C. albicans* at 200 μg/ml disc concentration and none of the other salicylic acid triazoles were active against the tested bacteria and fungi at a disc concentration of 100 and 200 μg/ml. But all the salicylic acid triazoles were highly active against *S. aureus* and *E. coli* of bacteria and fungi *C. albicans* at a disc concentration of 500 μg/ml. In anthranilic acid triazole compounds, 4C was found weakly active against both *S. aureus* and *E. coli* but inactive against *C. albicans* at a disc concentration of 200 μg/ml. All the other anthranilic acid triazoles were inactive against both the organisms of bacteria and fungi at 100 and 200 μg/ml disc concentrations. But all the anthranilic acid triazoles were highly active against *S. aureus* and *E. coli* of bacteria and fungi *C. albicans* at a disc concentration of 500 μg/ml.

All the three series of 1,2,4-triazoles were highly active against both the organisms of bacteria and fungi at 500 μg/ml disc concentration. On comparing the three series of triazoles with one another, anthranilic acid series of 1,2,4-triazoles were found to be more active than salicylic acid and p-amino benzoic acid triazoles while p-amino benzoic acid triazoles and salicylic acid series of triazoles were similar in their activities.

Antitubercular agents, isoniazid, pyrazinamide, ethionamide and vitamin nicotinamide exhibited antimicrobial activities when they were incorporated in to the triazole ring system. Therefore necessary modifications have to be made to improve the potency of these nicotinamide incorporated triazole ring compounds so as to develop them in to clinically useful novel class of compounds that can posses significant antimicrobial activity and can also be used as a vitamin at the same time.

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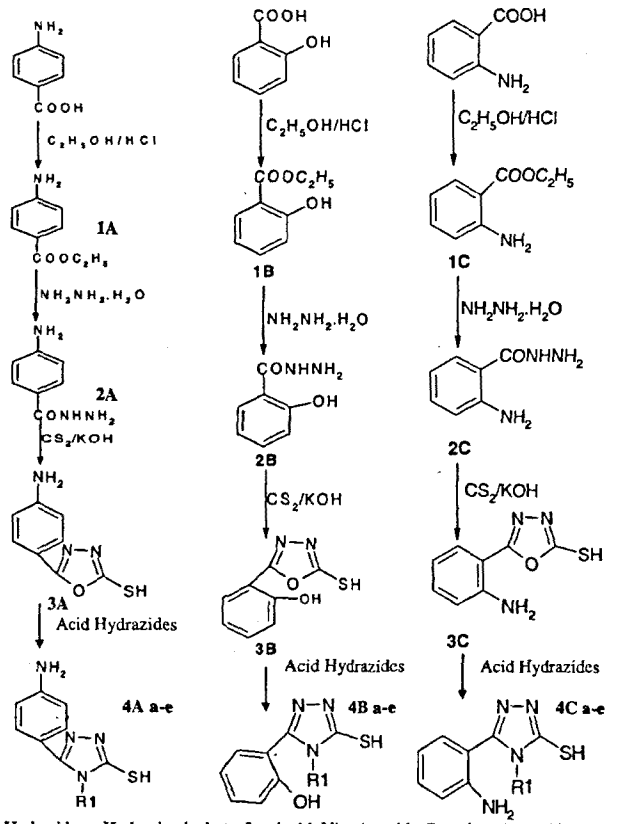
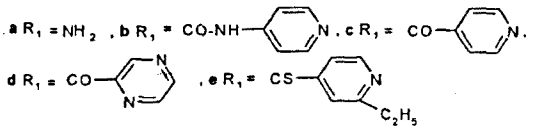


Acid Hydrazides = Hydrazine hydrate, Isoniazid, Nicotinamide, Pyrazinamide, Ethionamide



Scheme[10]

TABLE 1: CHARACTERIZATION DATA OF 1,2,4 - TRIAZOLES

Compounds	M.P.	% Yield	Molecular formula (molecular weight)	% Composition of C,H,N calculated (found)			Zone of inhibition in mm					
							Antibacterial activity				Antifungal activity	
							S.aureus		*E.coli*		*C.albicans*	
				C	H	N	200 µg/ml	500 µg/ml	200 µg/ml	500 µg/ml	200 µg/ml	500 µg/ml
4A a	211.9	82	$C_8H_9N_5S$ (207.26)	46.36 (46.09)	4.38 (4.36)	33.79 (33.6)	—	28	—	23	—	31
4A b	171.1	77	$C_{14}H_{12}N_6OS$ (312.36)	53.83 (53.8)	3.87 (3.82)	26.91 (26.8)	—	24	—	23	—	32
4A c	151.5	68	$C_{14}H_{11}N_5OS$ (297.34)	56.55 (55.12)	3.73 (3.02)	23.55 (21.67)	—	26	—	21	—	27
4A d	179.1	80	$C_{13}H_{10}N_6OS$ (298.33)	52.34 (52.3)	3.38 (3.35)	28.17 (28.14)	—	25	—	27	—	27
4A e	174.5	72	$C_{16}H_{15}N_5S_2$ (341.46)	56.28 (56.25)	4.43 (4.41)	20.51 (20.46)	—	21	—	25	—	25
4B a	177.1	69	$C_8H_8N_4OS$ (208.24)	46.14 (46.1)	3.87 (3.82)	26.9 (26.84)	—	20	—	27	—	30
4B b	166.1	86	$C_{14}H_{11}N_5O_2S$ (313.34)	53.67 (53.65)	3.54 (3.5)	22.35 (22.32)	—	27	—	25	—	22
4B c	170.8	62	$C_{14}H_{10}N_4O_2S$ (298.33)	56.37 (56.58)	3.38 (3.10)	18.78 (17.89)	—	28	—	25	13	26
4B d	180.7	82	$C_{13}H_9N_5O_2S$ (299.31)	52.17 (52.14)	3.03 (3.01)	23.4 (23.36)	—	31	—	23	—	21
4B e	178.3	75	$C_{16}H_{14}N_4OS_2$ (342.44)	56.12 (56.14)	3.38 (3.32)	18.78 (18.8)	—	25	—	21	—	20
4C a	175.7	78	$C_8H_9N_5S$ (207.26)	46.36 (46.35)	4.38 (4.37)	33.79 (33.74)	14	31	15	32	—	30
4C b	167.4	80	$C_{14}H_{12}N_6OS$ (312.36)	53.83 (53.8)	3.87 (3.82)	26.91 (26.89)	—	25	—	23	—	28
4C c	140.1	65	$C_{14}H_{11}N_5OS$ (297.34)	56.55 (56.18)	3.73 (3.07)	23.55 (23.11)	—	29	—	25	—	25
4C d	176.4	87	$C_{13}H_{10}N_6OS$ (298.33)	52.34 (52.3)	3.38 (3.31)	28.17 (28.13)	—	29	—	31	—	23
4C e	165.9	70	$C_{16}H_{15}N_5S_2$ (341.46)	56.28 (52.25)	4.43 (4.4)	20.15 (20.53)	—	27	—	29	—	31

Recrystallization solvent used is methanol, Solvent system used for TLC is benzene:methanol:DMF (8:1:1). For Antimicrobial screening 5 mm sterile disc paper was used.

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Fast Dissolving Rofecoxib Tablets

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Inclusion complex of rofecoxib, an NSAID with β-cyclodextrin using ball milling technique has been prepared and evaluated using DSC. The fast dissolving tablet composition with 25 mg equivalent rofecoxib showed complete release of rofecoxib in 12 min as compared to 20% drug release from the conventional release marketed tablets during the same period. The stability studies conducted as per ICH guidelines at 40° and 75% RH showed insignificant loss in drug content at the end of six months.

Pain is an unpleasant sensation and demands instant relief. Pharmacologic management has been the main stay of treatment for many pain syndromes. A major group of drugs used in pain management are nonsteroidal antiinflammatory drugs (NSAIDs), which also have analgesic and antipyretic associated activities. These NSAIDs relieve pain by, cyclooxygenase (prostaglandin synthetase) inhibition[1].

The rapid relief of pain sensation would depend on rapidity of absorption of NSAID, which, in turn, is governed by its dissolution rate. The drug delivery system involving fast dissolving dosage forms are well established in the management of pain therapy (e.g. nimesulide, piroxicam). Several methods have been reported for preparing fast dissolving dosage forms[2]. These necessarily use drug in water-soluble form. The water-insoluble drugs need manipulation to make them water-soluble. Among different approaches for solubilization[3-5], formation of inclusion complexes with non-toxic excipients such as cyclodextrins (CDs) is the most common approach used in practice[6-8]. This paper reports the preparation of β-CD complex of rofecoxib, a water-insoluble drug and its incorporation in a fast dissolving tablet dosage form.

Rofecoxib was obtained from Virdev Chemicals, β-CD was obtained from Cerestar, USA, PVP-K30 and Kollidon CL (Crospovidone) were obtained from BASF Corp., Germany, Avicel pH 102 (MCC) and Nymcel ZSX (Croscarmellose sodium) were obtained from FMC Corp., USA, Hyswell (Sodium starch glycolate) was obtained from Maruti Chemicals and Aerosil (200#) was obtained from Degussa Corp., Germany. Lactose, talc and starch used in the investigation were of IP grade. Conventional release marketed rofecoxib tablets representing 25 mg drug per tablet were obtained for comparison purposes. All these above chemicals were used as received. All other reagents and chemicals employed were of AR/GR grade or of the highest purity.

Rofecoxib and β-CD in molar ratios of 1:1, 2:3 and 1:2 were blended in a cone blender for 5 min (batch size 2.5 kg), wetted with adequate amount of water to achieve paste consistency and milled in a porcelain ball-mill (capacity 5.0 kg; 12 balls with diameter of 1.5 cm) for 36 h. The paste was dried in an oven at 45°, and sifted through 120# sieve. The

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