Asian Journal of Chemistry Vol. 17, No. 1 (2005), 631–633

NOTE

Synthesis and Biological Activities of Glycolamide Esters of Cinmetacin

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Glycolamide esters of cinmetacin (1-cinnamoyl-5-methoxy-2-methyl indole-3-acetic acid) with dimethylamine, diethylamine and morpholine were synthesized. They were screened for anti-inflammatory, analgesic and ulcerogenic activities. All of them were found to have biological activities comparable with parent drug and reduced side effect of ulceration.

Key Words: Synthesis, Cinmetacin, Glycolamide, Antimicrobial activities.

Cinmetacin (1-cinnamoyl-5-methoxy-2-methyl indole-3-acetic acid), derived from indomethacin, is used as an analgesic and antiinflammatory agent. The major side effect of the drug is gastric ulceration[1].

The present investigation is aimed at minimizing the side effect, with maintaining the analgesic, antiinflammatory activities and improving the physicochemical parameters. It was decided to synthesize and characterize the glycolamide esters of cinmetacin and evaluate for biological activity.

All reagents were of analytical reagent grade unless otherwise stated. Cinmetacin was procured from M/s Chiesi Farmaceutici, S.P.A., Parma, Italy.

The glycolamide ester were synthesized in two steps[2]:

1. Preparation of disubstituted 2-chloroacetamide by reacting 2-chloroacetyl chloride with respective amine in ethylacetate, in the presence of triethylamine.
2. Preparation of glycolamide esters by reacting cinmetacin with disubstituted 2-chloroacetamides of respective amines in dimethylformamide in presence of sodium iodide and triethylamine.

The compounds synthesized were purified by repeated washing with 2% sodium thiosulphate, 2% sodium bicarbonate and distilled water and recrystallized by using a mixture of hexane and ethylacetate. The IUPAC name, molecular weight, percentage yield, m.p., R_f values are given in Table-1.

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TABLE-1
GLYCOLAMIDE ESTERS OF CINMETACIN

Physical characteristics	Drug (CN)	Synthesized compound		
		CNGM	CNGE	CNMO
IUPAC	1-cinnamoyl-5-methoxy-2-methyl-3-indolyl acetic acid	1-cinnamoyl-5-methoxy-2-methyl-3-indolyl acetoxy-N',N'-dimethyl acetamide	1-cinnamoyl-5-methoxy-2-methyl-3-indolyl acetoxy-N',N'-diethyl acetamide	1-cinnamoyl-5-methoxy-2-methyl-3-indolyl acetoxymorpholino-diyl acetamide
m.w.	349	433	462	476
% yield	—	69.2%	72.1%	65.3%
m.p.*	164–165°C	98°C	83°C	80C°
R_f value	0.4305	0.5178	0.8880	0.9641

*Melting points were taken in open capillary tube and are uncorrected.

Biological Evaluation: The compounds synthesized were amorphous and insoluble in water, therefore all biological testings were carried out as homogenized suspension in 2% w/v gum acacia. Albino rats (Haffkine strain) were used for the experiments. The synthesized compounds were taken in equimolar quantities.

Antiinflammatory Activity: Test was performed by the procedure reported by Winter *et al.*[3] The oedema was induced in albino rats in a group of six rats by injecting 0.1 mL carrageenin into subplantar region of the left hind paw. The volume of paw was measured by using plethysmometer immediately after carrageenin injection and again after 4 h. The test compounds and cinmetacin were administered orally 1 h prior to carrageenin injection. Mean increase in paw volume and standard error (S.E.) were calculated and the results were expressed as % inhibition of oedema.

Analgesic Activity: Test was performed by tail flick method using Techno Analgesiometer[4]. The synthesized compounds and cinmetacin were administered orally at equimolar doses. The increase in reaction time and standard error (S.E.) were calculated and results were expressed as % change in analgesic activity.

Ulcerogenic Activity: The method reported by Cioli *et al.*[5] was used. The synthesized compounds and cinmetacin were administered orally after starvation for 18 h. After drug administration the rats were sacrificed and stomachs were removed and fixed in 10% formalin, then they were opened and examined by 2×2 binocular to measure number of lesions. Results are shown as % decrease in number of lesions.

Persual of Table-2 reveals that all glycomide esters exhibited analgesic and anti-inflammatory activity comparable with cinmetacin The major side effect, *i.e.*, gastric ulceration activity, was found to be reduced markedly. This indicates that blocking of free —COOH group has reduced the ulcerogenic activity.

TABLE-2
BIOLOGICAL ACTIVITY STUDIES OF GLYCOLAMIDE ESTERS OF CINMETACIN

Compound code	% Anti-inflammatory activity				% Analgesic activity				% Ulcerogenic activity
	1 h	2 h	3 h	4 h	30 min	60 min	90 min	120 min	
CN	52.94	51.15	50.78	49.12	79.48	77.85	76.20	75.34	80.0
CNGM	50.02	49.97	49.37	49.07	71.87	70.56	69.92	69.02	33.3
CNGE	51.08	50.87	50.05	49.10	73.30	72.20	71.65	70.39	29.1
CNMO	51.98	50.96	50.07	49.08	70.89	69.87	69.01	68.34	18.9

However, further studies (toxicity, LD_{50}) should be carried out to ascertain the usefulness of these compounds as better analgesic and antiinflammatory agents.

ACKNOWLEDGEMENT

The authors thank M/S Chiesi Farmaceutici, S.P.A., Parma, Italy for providing the drug sample.

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(*Received*: 26 April 2004; *Accepted*: 29 September 2004) AJC-3584