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Short communication

Synthesis of some novel imidazolinones as potent anticonvulsant agents

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Abstract

Imidazolinone derivatives of **IIa**–**IIc**, **IIIa**–**IIIf** and **IVa**–**IVf** have been synthesised by the condensation of some known sulpha drugs with 5-oxazolone derivatives, which were prepared by Erlenmeyer condensation of benzoyl glycine with different aldehydes in the presence of sodium acetate and acetic anhydride. The constitution of the products has been supported by elemental analysis and IR, ^{1}H-NMR spectral data. The products have been screened for their (a) in vitro growth inhibitory activity against several microorganisms and (b) in vivo anticonvulsant activity.

Keywords: Imidazolinones; Oxazolone; Sulpha drugs; Antibacterial anticonvulsant agent

1. Introduction

Literature survey reveals that various imidazolinone derivatives possess a broad spectrum of pharmacological actions which are reflected by their use as anticonvulsant [1], anti-Parkinsonian [2] and monoamine oxidase (MAO) inhibitory [3] agents. Some novel disubstituted imidazolinones were investigated as anticonvulsant, MAO and succinate dehydrogenase (SDH) inhibitory agents [4]. So, it was thought worthwhile to synthesise various imidazolinones and to evaluate them for their anticonvulsant activity.

2. Chemistry

Some new imidazolinone derivatives (**IIa**–**IIc**, **IIIa**–**IIIf** and **IVa**–**IVf**) (Scheme 1) bearing sulphonamide moiety have been synthesised by the condensation of some known sulpha drugs with oxazolones of different aromatic aldehydes. Intermediates 4-arylidene-2-phenyl-5-(4*H*)-oxazolones (**Ia**–**Ic**) were prepared by the condensation of aryl aldehyde with benzoyl glycine in the presence of sodium acetate and acetic anhydride (Erlenmeyer oxazolone condensation). The constitution of the products was supported by elemental analysis and spectral data. The products were screened for their in vitro growth inhibition activity against different Gram-positive and Gram-negative bacterial strains.

Identification of pharmacophore and its verification have always been the subject of interest to medicinal chemist. The therapeutic importance of imidazolinones has been reported [5,6]. Sulpha drugs are potent antibacterial agents [7–12]. A study on the influence of structure on activity shows that variation in ring systems or minor group modifications confer distinct pharmacological effects upon the drug molecules.

3. Pharmacology

3.1. Antimicrobial activity

The activity was determined using cup-plate agar diffusion method [13] by measuring the inhibition zones

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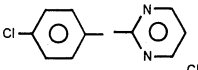
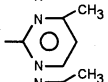
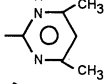
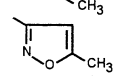
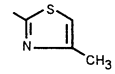
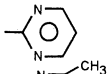
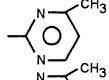
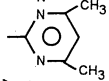
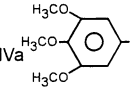
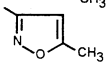
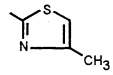
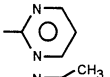
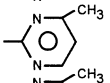
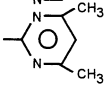
Table 1
Anticonvulsant and antimicrobial activity of compounds **1**–**15**

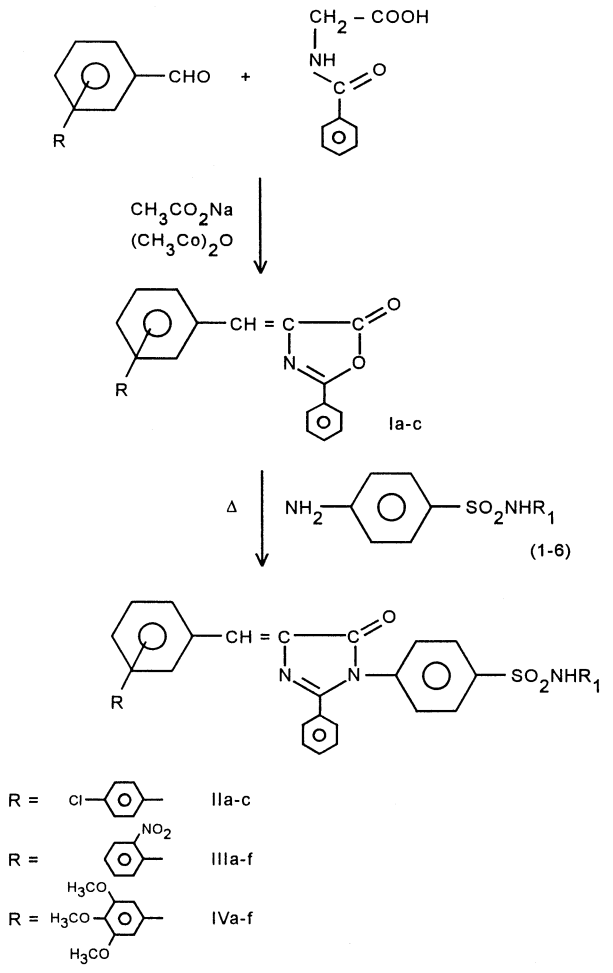
	R	R1	Mol. Formula	M.P.	Anticonvulsant activity		Antibectarial activity*			Antifungal activity*		
				°C	Protection%	mortality%	S.A.	B.M.	E.C.	Ps.F.	A.F.	C.A.
IIa			$C_{26}H_{18}N_5O_3SCl$	111	40	60	+++	+++	+	+++	+	++
IIb			$C_{27}H_{20}N_5O_3SCl$	191	70	20	++	+	+	++	+	++
IIc			$C_{28}H_{22}N_5O_3SCl$	166	--------N. S.-------		+	++	+	+++	++	+
IIIa			$C_{26}H_{19}N_5O_6S$	145	40	20	+	+	++	+	++	+
IIIb			$C_{26}H_{19}N_5O_5S_2$	148	80	40	+	++	+	++	+	++
IIIc		$-COCH_3$	$C_{24}H_{18}N_4O_6S$	151	80	20	++	+	++	+++	++	+
IIId			$C_{26}H_{18}N_6O_5S$	166	60	20	+	++	+	++	+++	++
IIIe			$C_{27}H_{20}N_6O_5S$	195	40	20	++	++	+	++	+	++
IIIf			$C_{28}H_{22}N_6O_5S$	170	60	40	++	++	+	++	+	++
IVa			$C_{29}H_{26}N_4O_7S$	148	80	20	++++	+	++++	++++	++	+
IVb			$C_{29}H_{26}N_4O_6S_2$	68	--------N. S.-------		++	+	+++	++	+	+++
IVc		$-COCH_3$	$C_{27}H_{25}N_3O_7S$	90	80	20	++	+	+++	+++	++	++
IVd			$C_{29}H_{25}N_5O_6S$	72	60	40	+	++	+++	+++	+++	+
IVe			$C_{30}H_{27}N_5O_6S$	48	70	20	++	+	++	+++	+	++
IVf			$C_{31}H_{29}N_5O_6S$	82	40	60	+	++	+	+	++	++
1	Phenobarbitone				100	Nil	-	-	-	-	-	- -
2	Ampicillin			-	-	-	+++	+++	+++	+++	+++	+++
3	Norfloxacin			-	-	-	+++	+++	++	++	+++	++
4	Sulphacetamide Na			-	-	-	++	++	+++	++++	+++	++
5	Greseofulvin			-	-	-	+++	++	++	++++	+++	+++
6	DMF			-	-	-	+	+	+	+	+	+

All Compounds gave satisfactory C,H,N,S, analyses. yield range 51-80%. #N.S.=Not Screened

*S.A.=Staphylococcus aureus; B.M.=Basilius Mageterium; E.C.=Eschenchia coli: Ps.F.=pseudomonas Flourescens; A.F.=Aspergillius Flavus; C.A.=Candida albicans;

*Zone of inhibition after 24hrs - 10-15 mm.= +, 16-20 mm. = ++, 21-25 mm. = +++, 26-35 mm. = ++++, D.M.F. = +

in millimetres. All the compounds were screened in vitro for their antimicrobial activities against a variety of bacterial strains such as *Staphylococcus aureus*, *Bacillus megaterium*, *Escherichia coli*, *pSeudomonas fluorescens* and fungi such as *Aspergillus flavus* and *Caudida albicans*. Known antibiotics like ampicillin, norfloxacin sulphacetamide and gresiofluvin were used for comparison. Most of the compounds exhibited maximum activity in the range 17–33 mm against *P. fluorescens*. Compounds **IIa**, **IIIb**, **IIIf** and **IVb** showed highest



Scheme 1.

activity (20–33 mm) against above microbes. Other compounds showed moderate activity (18–25 mm) against these organisms.

3.2. Anticonvulsant activity

Out of 15 compounds (Table 1), 13 compounds were screened for their in vitro anticonvulsant activity [14]. It appears that compounds **IIb**, **IIc** and **IVf** were most effective with highest protection and minimum mortality rate. Compounds **IIa**, **IIIb** and **IIIe** displayed significant activity (80% protection) while most of the compounds exhibited moderate activity.

3.3. Toxicity test

Approximate lethal doses (ALD_{50}) of the compounds were determined in albino mice following reported method [15]. ALD_{50} values of these compounds were in the range 300–900 mg kg^{-1} i.p. This indicates their low toxicity.

These observations led to the conclusion that the presence of $-CH_3-$ or $-OCH_3-$ group increases the pharmacological activity.

4. Experimental protocols

4.1. Chemistry

All the recorded melting points were determined in open capillary tubes and are as observed. Completion of the reaction was monitored by TLC (silica gel GF_{254} (E. Merck), benzene:ethyl acetate = 80:20). The final products were purified by column chromatography using silica gel in increasing percentage of ethyl acetate in benzene. IR (KBr) (ν_{max}, cm^{-1}) spectra were recorded on SHIMADZU-435 IR spectrophotometer. ^{1}H-NMR spectra were recorded on Varian EM-360 spectrometer wear in δ ppm, relative to TMS as internal standard. Elemental analyses are quite comparable with their structures. In all cases, analytical values for microanalysis were $\pm 0.05\%$ of theoretical values.

4.1.1. 4-Arylidene-2-phenyl-5-(4H)-oxazolones

4-Arylidene-2-phenyl-5-(4*H*)-oxazolones were prepared according to the reported method [16] (**Ia**–**Ic**).

4.1.2. 1-N-substituted sulphonyl amino-2-phenyl-4-substituted benzylidene-5-imidazolinones (*II*, *III* and *IV*)

2-Phenyl-4-benzylidene-5-oxazolone (2.49 g, 0.01 mol) was heated with an equimolar quantity of sulphacetamide (2.14 g, 0.01 mol) in an oil bath at 140 °C for 1 h. The resulting jelly-like mass was taken in an organic solvent and refluxed for 8 h with continuous removal of water, cooled, excess solvent removed under vacuum and the resultant solid was worked up and purified over a column of silica gel, and the solid recrystallised from light petroleum to get flakes of 5-imidazolinone and found chromatographically homogeneous when detected with iodine in 62% yield, m.p. 148 °C. Similarly, other compounds were also synthesised by this method. Found: C, 72.95; H, 4.90; N, 13.60; for $C_{14}H_{19}N_3O_4S$ required C, 73.00; H, 4.94; N, 13.64%.

IR (KBr) ν_{max} (cm^{-1}): 3020–3100 (Ar–CH), 3000–2910 (C=C str.), 1750 (C=O str.), 1640 (C=N str.), 1320, 1150 (S=O str.), 1180 (C=O str.).

^{1}H-NMR (DMSO-d_6, d) 2.42 (s, 3H, $COCH_3$), 6.4 (s, 1H, C=CH), 7.1–7.6 (m, 14H, Ar–H), 8.1 (s, H, SO_2NH).

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