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2-((4-oxo-2-thiazolidin-5-ylidine) methyl) phenoxy) acetamides as anticonvulsant agents

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ABSTRACT

A new series of (Z)-N-(substitutedphenyl)-2-(2-((4-oxo-2-thiazolidin-5-ylidine) methyl)phenoxy)acetamides (d_{1-8}) have been synthesized by reaction of 2-thioxo-4-thiazolidinone(a) with salicyldehyde and vanilline, which upon O-alkylation with different chloro - acetamides (c_{1-4}) form the final derivatives (d_{1-8}). The physical and spectral data of synthesized compounds are determined. The synthesized compounds have been screened for their anti-convulsant activity by MES method.

Key words: Acetamides, Anti-convulsant activity, MES method

INTRODUCTION

During the past years, considerable evidence has been accumulated to demonstrate the efficacy of 2-thioxo-4–thiazolidinone and acetamide derivatives. 2-thioxo-4–thiazolidinone based molecules have been popular as small molecule inhibitors of numerous targets such as anti-convulsant agents[1,2], anti-diabetic agents[3], anti-microbial agents[4] and histidine decarboxylase[5].

Dry ammonia and carbon disulphide in alcohol and ether combined to form ammonium dithiocarbamate, which react with sodium chloroacetate to form rhodanine[6](a). Rhodanine on condensation with salicyldehyde and vanilline form hydroxy benzylidine rhodanine[6](b_1 and b_2). These key intermediates upon O-alkylation with different chloro acetamides (c_{1-4}) form final derivatives (d_{1-8})[7]. The title compounds (c_{1-4}) have been synthesized via various aromatic amines with chloro acetyl chlorides in acetic acid [8]. The physical properties of compounds are presented in Table.1 and Table.2.

MATERIAL AND METHODS

All the chemicals used were AR grade and some were LR grade, procured from various chemical units like Merck, Mumbai, Qualigens, Mumbai; s.d.Fine, Mumbai and CDH-New Delhi. Melting points were determined in open glass capillaries and are uncorrected. The I.R. spectra (KBr disc) were recorded on FTIR-200 Thermo Electron Corporation .^{1}H-NMR spectra were recorded in DMSO using BRUKER AVANCE II 400 NMR spectrometer. The chemical shifts were expressed in δ units in ppm downfield from TMS. The purity and completion of reaction was monitored by TLC using benzene: ethyl acetate, 4:1 solvent system and silica gel-G coated on glass plates used as solid support.

Synthetic study

The scheme of 2-((4-oxo-2-thiazolidin-5-ylidine) methyl) phenoxy) acetamide analogues is given in Fig.1

Synthesis of rhodanine[6] (a)

Dry ammonia passed through an ice-cooled mixture of carbon disulphide (30ml), alcohol (24ml) and ether (24ml) for a period of about 3.5 hrs. The content of flask solidified into a pale yellow cake i.e. ammonium dithiocarbamate. This was further washed with alcohol (5ml), followed by ether (10ml). This was immediately added to a solution of sodium chloroacetate with stirring which in turn prepared by mixing of sodium hydroxide (0.5mol) and chloroacetic acid (0.5mol), the mixture was cooled to 0°C . At first the solution become dark but on further stirring mixture turned straw like. The above content then finally added to the 36ml of conc. HCl. The mixture was heated to 80°C for 2min., and then placed the flask to an ice bath for 1hr., glistening pale yellow crystals of rhodanine separated out, filtered and washed with little water and finally recrystallized from alcohol. Yield - 65%; m.p - 169°C; I.R. Data – 1713(C=O), 1185(C=S), 3091(NH), 1234(C-N), 2839(C-H).

Synthesis of hydroxy benzylidine rhodanine[6] (b_1 and b_2)

Rhodanine (0.02mol) added to the preheated 50ml glacial acetic acid and mixed well to dissolve completely. To this, was added salicyldehyde, for b_1, (0.02mol) or vanilline, for b_2, (0.02mol) and fused sodium acetate (1.8g). The completion of reaction was controlled by TLC analysis, and completed in about 45min. The content was then poured in about 1000ml of cold water, the yellow precipitate was separated out, filtered and

Table 1: Characterization data of synthesized compounds c_{1-4}

Compd.	Yield (%)	m.p (°C)	R_f	IR data
c_1	76	116	0.57	Ar.C-H 3076, Ali.C-H 2834, -CONH 1669,-NH 3264, C-N 1395, Ar.C=C 1511
c_2	60	73	0.56	-
c_3	70	126	0.72	-
c_4	53	150	0.45	Ar.C-H 3010, Ali.C-H 2838, -CONH 1667-NH 3295, C-N 1345, Ar. C=C 1512

Table 2: Characterization data of synthesized compounds d_{1-8}

Compd.	Yield (%)	m.p (°C)	R_f	^{1}H NMR data
d_1	48	256	0.14	Ar-H(m,6.94-7.66),-NHCO- (s,10.01),ring-NH-(s,13.4),-CH=(s,8.07)
d_2	52	248	0.12	-
d_3	42	278	0.16	Ar-H(m,6.94-7.62),-NHCO-(s,10.03),ring-NH-(s,13.2),-CH=(s,7.98),-OCH_3(s,4.01)
d_4	44	284	0.13	-
d_5	56	242	0.17	Ar-H(m,6.94-7.62),-NHCO-(s,10.03),ring-NH-(s,13.2),-CH=(s,7.98),-OCH_3(s,4.01)
d_6	47	262	0.22	-
d_7	41	269	0.15	Ar-H(m,6.94-7.62),-NHCO-(s,10.03),ring-NH-(s,13.2),-CH=(s,7.98),-OCH_3(s,4.01)
d_8	54	272	0.20	-

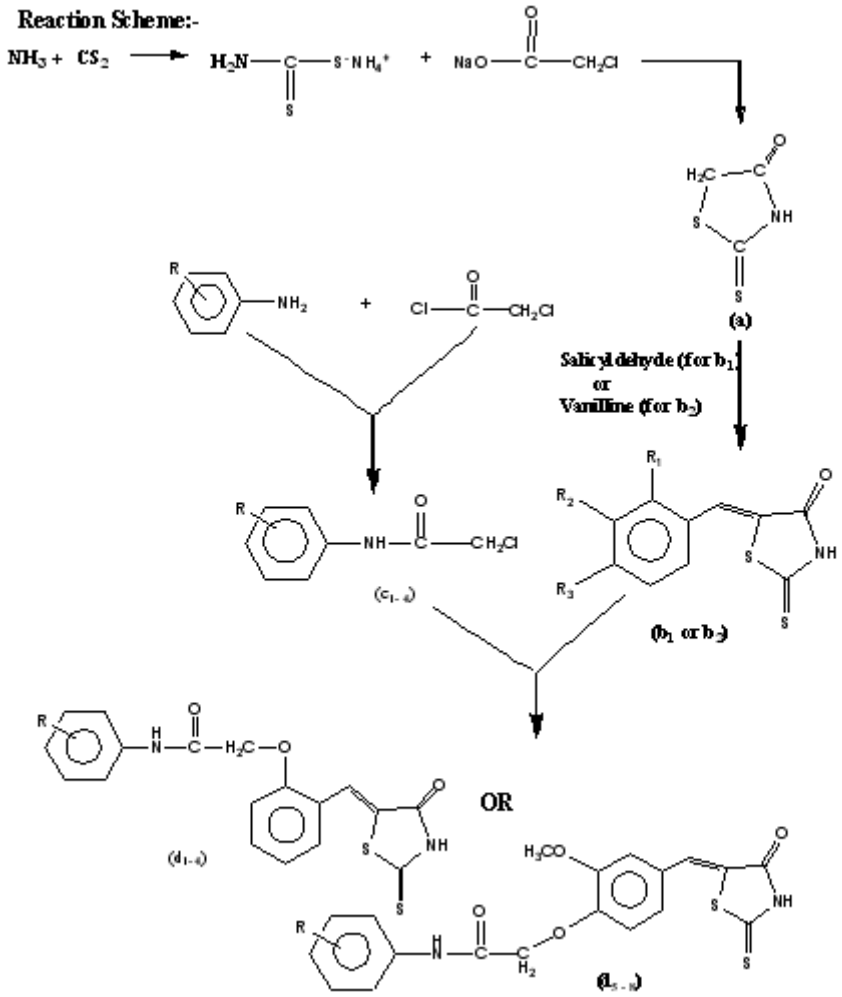
washed with cold water, dried and recrystallised from glacial acetic acid. (b_1) - Yield – 72%; m.p. - 236°C; IR Data- 1694(C=O), 1185(C=S), 1249(C-N), 3170(N-H), 3414(O-H), 1522(C=C), 2910(C-H); (b_2) - Yield – 83%; m.p. - 257°C; IR Data- 1703 (C=O), 1163(C=S), 1232(C-N), 3188(N-H), 3452(O-H), 1536(C=C), 2887(C-H), 1076(C-O).

General procedure for synthesis of chloroacetamides[8] (c_{1-4})

Aromatic amines (0.01mol) were dissolved in 10ml of glacial acetic acid containing 50ml of saturated solution of sodium acetate. The solution was cooled in an ice bath and chloroacetyl chloride (0.01mol) was added dropwise to the mixture. The white precipitate separated was filtered, washed with 50% acetic acid and recrystallised from ethanol (Table.1).

General procedure for synthesis of d_{1-8}[7,8]

The compounds c_{1-4} (0.01mol) were dissolved in ethanol (10ml), triethylamine (0.01mol) was added to the solution. To this reaction mixture 0.01mol of (b_1), for (d_{1-4}), or 0.01 mol of (b_2), for



Compound	R_1	R_2	R_3
b_1	-OH	-H	-H
b_2	-H	$-OCH_3$	-OH

Fig. 1: R = 0-chloro phenyl, -chlorphenyl, o-bromophenyl, p-bromophenyl

(d_{5-8}), was added. The reaction mixture was refluxed and completion of reaction was controlled by TLC analysis, usually completed in about 18-20 hrs. Cooled the reaction mixture, added ice pieces to it and little distilled water, then the product was extracted with ethyl acetate twice, 25ml each time. The ethyl acetate was removed under vacuum to provide crude d_{1-8} which then recrystallised from ethanol (Table.2).

In-vivo study

Acute toxicity study

All the compounds were screened for acute oral toxicity study according to OECD guidelines[9]. The compounds synthesized d_{1-8} were found to have LD_{50} in range 500-600mg/kg b.w. in female mice.

Anti-convulsant studies

The compound d_{1-8} were screened for their anti-convulsant activity against electroshock-induced convulsion in mice of either sex (weighing 20-30g) by the method given in literature[10]. The compounds were suspended in 5% gum acacia solution and given orally at a dose of 50mg/kg b.w. After 1hr. the animals subjected to a current of 60mA/ 50Hz for 0.2sec. and the effect was observed. Compounds $d\text{-}_1$, d_2, d_3, d_4, d_5, d_6, d_7 and d_8 provided 95,70,60,73,57,78,66 and 85% protection respectively against the electroshock-induced convulsion in mice compared to 100% activity of phenytoin (a reference drug) at a dose of 25mg/kg b.w.

RESULT AND DISCUSSION

In present study the compounds $d\text{-}_{1-6}$ were synthesized and their physical and spectral analysis was done. Their purity was checked by TLC that gave satisfactory results. The compounds synthesized reflects remarkable anti-convulsant activity by MES method at a lower dose i.e. 50mg/kg b.w. The compounds showed lower toxicity than parent compound (b).

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REFERENCES

1. Misra.S., Srivastava.S.K., Srivastava.S.D., *Indian J. Chem*. Sec. B,**36**: 826 (1997)
2. Troutman.H.B., Long. L.M., *J. Am. Chem. Soc.*, **70**: 3436 (1948)
3. Panetta.Jill A., Juliana. M., Jones. C.D., Hunden. D.C.,Bue-Vallesky, Shaw.W.N., United State Patent,US 5, 661,168, 26th Aug.,(1997)/*Chem.Abst.*,**125**:117581, (1997).
4. Donia. S. G.,*J .P harm. Sci.*, **34**: 521 (1994)
5. Free. C.A., Majchrowicz. E.,Hess. S. M., *Biochem. Pharm.*, **20**: 1421 (1971)
6. Singh.S.P.,Parmar.S.S., Raman.K., Stenberg. V.I., *Chem. Rev.*,**81**: 175 (1981)
7. Furniss.B.S., Hannaford. A.J., Smith. P.W.G., Tatchell.A.R., *Vogel's Textbook of Practical Organic Chemistry*,Ed.5th , Longmann Group Limited, London, 984 (1989)
8. Bhosale.S.H.,Rode.M.S.,Basgare.S.S., Gawai.A.A.,Bhosale.M.S.,Mahadik.K.R. and Kadam.S.S.,*Indian J. Hetro. Chem.*, **15**: 267 (2006)
9. Acute Oral Toxicity Guidelines for testing of chemicals, 423,adopted 17Dec.2001
10. Grover.J.K., *Experiments in Pharmacy and Pharmacology*, Vol.II, Ed.Ist,CBS,New Delhi, 162 (1990)