Synthesis and biological evaluation of 3-aryloxyalkyl-6-aryl-7H-s-triazolo[3,4-b][1,3,4]thiadiazines

ARTICLE *in* EUROPEAN JOURNAL OF MEDICINAL CHEMISTRY · MARCH 1989

Impact Factor: 3.45 · DOI: 10.1016/0223-5234(89)90116-5

Indian Journal of Chemistry
Vol. 25B, May 1986, pp. 566-568

Synthesis & Biological Activity of 2-Aryloxyalkyl-5-(3,4-methylenedioxyphenyl)-*s*-triazolo[3,4-*b*]-1,3,4-thiadiazoles

A R PRASAD, T RAMALINGAM, A BHASKAR RAO, P V DIWAN & P B SATTUR*

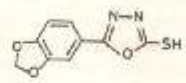
Medicinal Chemistry and Natural Products Division
Regional Research Laboratory,
Hyderabad 500 007

Received 15 July 1985; accepted 26 August 1985

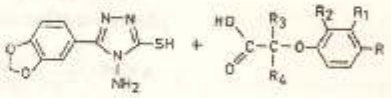
4-Amino-5-mercapto-3-(3,4-methylenedioxyphenyl)-1,2,4-triazole (II) reacts with various aryloxyalkyl carboxylic acids to yield 2-aryloxyalkyl-5-(3,4-methylenedioxyphenyl)-*s*-triazolo[3,4-*b*]-1,3,4-thiadiazoles (III). Interesting profiles of analgesic and anti-inflammatory activities have been observed during primary screening of these compounds in experimental animals.

In our earlier work[1,2] we found that 2,5-disubstituted-*s*-triazolo-[3,4-*b*]-1,3,4-thiadiazoles possess strong CNS depressant, mild to moderate antiinflammatory and mild hypocholesteremic and hypotensive activities. Incorporation of appropriate aryloxyalkyl moiety in heterocyclic rings[3] such as oxadiazole and *s*-triazole has led to the compounds possessing CNS depressant, antiinflammatory and hypotensive actions. In view of antiinflammatory and antipyretic activities exhibited by compounds containing methylenedioxyphenyl group[4], we attempted to study the effect on biological activity of methylenedioxyphenyl moiety attached to a *s*-triazolothiadiazole ring. These observations prompted us to synthesise 2-aryloxyalkyl-5-(3,4-methylenedioxyphenyl) *s*-triazolo-[3,4-*b*]-1,3, 4-thiadiazoles (III) and screen them for their analgesic and antiinflammatory activities.

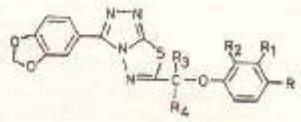
The synthesis of III was accomplished in one step with good yields by condensing 4-amino-5-mercapto-3-(3,4-methylenedioxyphenyl)-1,2,4-triazole (II) with various aryloxyalkyl carboxylic acids in the presence of phosphorus oxychloride (Scheme 1). The *s*-triazole II, in turn was prepared from the corresponding 1,3,4-oxadiazole (I) following the method of Heindel[5]. The characterisation data of III and their biological activity are given in Tables 1 and 2 respectively.



I



II



III (1–15 : Table 1)

R = H or Cl, R_1 = H, R & R_1 = O-CH_2-O

R_2 = H, CH_3 or Cl, R_3 & R_4 = H or CH_3

Scheme 1

Primary screening results

Toxicity (LD_{50}), analgesic and antiinflammatory activities of compounds III in experimental animals were determined by literature methods[6,7]. All the compounds along with the starting material were devoid of toxicity as shown by their LD_{50} values which were more than 800 mg/kg oral (i.p. mice). It can be observed from Table 2 that compounds III_{13} and III_{15} exhibit analgesic activity (i.e. 60% and 58% respectively) similar to that of aspirin (60%) whereas the starting triazole (II) shows only 10% analgesic action. Compound III_{14} exhibits mild antiinflammatory activity (24%) in comparison to phenyl butazone (39%), while triazole II shows 15% anti-inflammatory action.

It has been reported earlier[1] that 2-phenoxymethyl-5-phenyl-*s*-triazolo[3,4-*b*]-1,3,4-thiadiazole exhibits 11% analgesic and 10% antiinflammatory activities. However, in the present study the corresponding 2-phenoxymethyl-5-(3,4-methylenedioxyphenyl)-*s*-triazolo[3,4-*b*]-1,3,4-thiadiazole (III_1) exhibited 21% analgesic activity and 15% antiinflammatory activity. This shows that the incorporation of a 3,4-methylenedioxy group in the phenyl ring does enhance the above activities.

The structural assignments of II and III were based on elemental analyses and IR, PMR and mass spectral data. All the compounds were checked for their purity by TLC on silica gel-G.

Melting points were taken in open capillaries on a Buchi 510 melting point apparatus and are

Table 1—Characterization Data of 2-Aryloxyalkyl-5-(3,4-methylenedioxyphenyl)-*s*-triazolo[3,4-*b*]-1,3,4-thiadiazoles (III)

Compd	R_2	R_3	R_4	m.p. °C	Yield (%)	Mol. formula	Found (%) (Calc.) C	H	N
				$R = R_1 = H$					
III_1	H	H	H	185	75	$C_{17}H_{12}N_4O_3S$	57.0 (56.9	3.5 3.4	15.8 15.9)
III_2	H	CH_3	H	108-10	72	$C_{18}H_{14}N_4O_3S$	59.1 (59.0	3.9 3.9	15.3 15.3)
III_3	H	CH_3	CH_3	103-5	68	$C_{19}H_{16}N_4O_3S$	61.6 (61.6	4.4 4.4	15.2 15.1)
				$R = Cl; R_1 = H$					
III_4	H	H	H	198-200	73	$C_{17}H_{11}ClN_4O_3S$	52.8 (52.8	2.9 2.9	14.5 14.5)
III_5	H	CH_3	H	110	74	$C_{18}H_{13}ClN_4O_3S$	54.0 (53.9	3.3 3.3	14.0 14.1)
III_6	H	CH_3	CH_3	98-100	67	$C_{19}H_{15}ClN_4O_3S$	55.1 (55.0	3.6 3.6	13.6 13.5)
III_7	Cl	H	H	178-80	71	$C_{17}H_{10}Cl_2N_4O_3S$	48.5 (48.5	2.4 2.4	13.3 13.3)
III_8	Cl	CH_3	H	158-60	69	$C_{18}H_{12}Cl_2N_4O_3S$	49.7 (49.7	2.8 2.8	12.9 12.9)
III_9	Cl	CH_3	CH_3	134-35	66	$C_{19}H_{14}Cl_2N_4O_3S$	50.9 (50.8	3.2 3.1	12.5 12.5)
III_{10}	CH_3	H	H	108-10	72	$C_{18}H_{13}ClN_4O_3S$	54.0 (53.9	3.3 3.3	14.0 14.0)
III_{11}	CH_3	CH_3	H	118-20	71	$C_{19}H_{15}ClN_4O_3S$	55.1 (55.0	3.7 3.6	13.6 13.5)
III_{12}	CH_3	CH_3	CH_3	143-45	66	$C_{20}H_{17}ClN_4O_3S$	56.1 (56.0	4.1 4.0	13.0 13.1)
				$R, R_1 = -O-CH_2-O-$					
III_{13}	H	H	H	220-21	71	$C_{18}H_{12}N_4O_5S$	54.6 (54.5	3.1 3.0	14.1 14.1)
III_{14}	H	CH_3	H	169-70	70	$C_{19}H_{14}N_4O_5S$	55.7 (55.6	3.5 3.4	13.7 13.7)
III_{15}	H	CH_3	CH_3	179-80	65	$C_{20}H_{16}N_4O_5S$	56.6 (56.6	3.8 3.8	13.2 13.2)

Table 2—Analgesic and Antiinflammatory Activities of Compounds II and III

(Dose 100 mg/kg oral)

Compd	Analgesic action (% protection of pain)	Antiinflammatory action (% inhibition)*
II	10	15
III_1	21	15
III_2	18	17
III_3	23	15
III_5	17	18
III_{12}	60	13
III_{14}	31	24
III_{15}	58	18
Aspirin	60	—
Phenylbutazone	—	39

*The compounds which possess inhibition less than 10% have not been shown in the table.

uncorrected. IR spectra were recorded on a Perkin-Elmer 221 spectrophotometer (ν_{max} in cm^{-1}), PMR spectra on a Varian A60A spectrometer using TMS as the internal standard (chemical shift in δ, ppm) and mass spectra on a Hitachi RMU 6L mass spectrometer at 70 eV.

4-Amino-5-mercapto-3-(3,4-methylenedioxyphenyl)-1,2,4-triazole (II)

A mixture of 2-mercapto-5-(3,4-methylenedioxyphenyl)-1,3,4-oxadiazole (5 g), hydrazine hydrate (15 ml) and ethanol (60 ml) was refluxed on a steam-bath for 13 hr. The reaction mixture was concentrated, poured into ice water and acidified with acetic acid to get the product which was filtered and recrystallised from ethanol, m.p. 214-15°, yield 4 g (75%) (Found: C, 45.8; H, 3.5; N, 13.6. $C_9H_8N_4O_2S$ requires C, 45.8; H, 3.4; N, 13.5%); IR(KBr): 3300 (NH_2), 3100 (NH), 1620 (C=N) and

1550 (C=C); PMR ($CDCl_3$): 6.10 (*s*, 2H, O-CH_2-O), 7.1-7.8 (*m*, 3H, Ar-*H*), 6.9 (broad, 1H, NH) and 5.7 (broad, 2H, NH_2). MS: *m/z* 236 (M^+), 205 ($M^+ - N_2H_3$), 165 ($M^+ - CH_3N_4$), 147 ($M^+ - CH_3N_3S$), 121 ($M^+ - C_3H_3N_4S$), 221 ($M^+ - NH$), 162 ($M^+ - CH_2N_2S$), 191 ($M^+ - CHS$), 178 ($M^+ - CNS$), 177 ($M^+ - CHNS$), 161 ($M^+ - CH_3N_2S$).

4-Chloro-2-methylphenoxymethyl-5-(3,4-methylenedioxyphenyl)-s-triazolo[3,4-*b*]-1,3,4-*thiadiazole* (III_{10})

A mixture of II (4.72 g; 0.02 mol), 4-chloro-2-methylphenoxyacetic acid (4.01 g; 0.02 mol) and $POCl_3$ (20 ml) was heated under reflux for 5 hr and excess $POCl_3$ removed under reduced pressure. The concentrated mass was cooled and poured into ice cold water to give a solid product which on washing with a dil. solution of $NaHCO_3$ followed by water and recrystallisation from ethanol gave the title compound III_{10}. IR (KBr): 1630 (C=N), 1230 (ether); PMR ($CDCl_3$): 2.35 (*s*, 3H, CH_3), 5.31 (*s*, 2H, OCH_2), 5.95 (*s*, 2H, O-CH_2-O), 6.50-7.15 (*m*, 4H, 3 Ar-*H* of 2-substituent and 1 Ar-*H* of 5-substituent), 7.75-7.90 (*m*, 2H, 2 Ar-*H* adjacent to C-N); MS: *m/z* 400 (M^+), 260 ($M^+ - C_7H_5ClO$), 259 ($M^+ - C_7H_6ClO$), 155 ($M^+ - C_{10}H_5N_4O_2S$), 147 ($M^+ - C_{10}H_8ClN_3OS$), 142 ($M^+ - C_{11}H_6N_4O_2S$), 125 ($M^+ - C_{11}H_7N_4O_3S$), 121 ($M^+ - C_{11}H_6ClN_4OS$), 113 ($M^+ - C_{12}H_7N_4S_2O_2$) and 107 ($M^+ - C_{11}H_6ClN_4SO_2$).

Compounds III_4-III_9 and III_{11}-III_{15} (Table 1) were prepared in a similar manner by the reaction of II with appropriate aryloxyalkyl carboxylic acids.

One of the authors (A R P) is thankful to the CSIR, New Delhi for the award of a senior research fellowship.

References

1 Mody M K, Prasad A R, Ramalingam T & Sattur P B, *J Indian chem Soc*, 59 (1982) 769.

2 Deshmukh A A, Mody M K, Ramalingam T & Sattur P B, *Indian J Chem*, 23B (1984) 793.

3 Ramalingam T, Deshmukh A A, Sattur P B, Sheth U K & Naik S R, *J Indian chem Soc*, 58 (1981) 269.

4 Mazzone G, Bonina F, Puglisi G, Cosentino C & Blandino G, *Farmaco Ed Sci*, 37 (1982) 685; *Chem Abstr*, 98 (1983) 100754r.

5 Reid J R & Deindel N D, *J heterocycl Chem*, 13 (1976) 925.

6 Sheth U K, Dadkar N K & Kamat U G, *Selected topics in experimental pharmacology* (M K Kothari, Bombay) 1972, 124.

7 Harris L S & Uhle F C, *J Pharmacol exptl Therap*, 132 (1961) 241.