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

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triazolothiadiazines / analgesic and anti-inflammatory activities

Introduction

The biological activities of various triazole derivatives [1–3] and thiadiazines [4, 5] have been extensively studied. It is observed from the literature that the *s*-triazole moiety has great versatility in fusing to various ring systems. Fused s-triazoles, such as *s*-triazolo[3,4-*a*]isoquinolines, *s*-triazolo-[4,3-*b*]-pyridazines and *s*-triazolo[4,3-*a*]benzodiazepines possess a broad spectrum of biological activities. Among the most important effects are: anti-inflammatory [6], hypotensive [7], analgesic and hypnotic [8] and anti-fungal [9] activities. However, triazolothiadiazines have not been investigated in detail. In our laboratory, we have synthesized and screened 2-aryloxyalkyl-5-(3,4-methylenedioxyphenyl)-*s*-triazolo[3,4-*b*]1,3,4-thiadiazoles for their analgesic and anti-inflammatory profiles [10]. The present study, undertaken as a result of the aforementioned facts, is concerned with the synthesis of 3-aryloxyalkyl-6-aryl-7*H*-*s*-triazolo[3,4-*b*][1,3]thiadiazines to be tested as potential analgesic and anti-inflammatory agents.

Chemistry

For the synthesis of title compounds, 4-amino-3-aryloxyalkyl-5-mercapto-1,2,4-triazoles **3** required as starting materials were prepared by the reaction of aryloxyalkyl carboxylic acids **1** with thiocarbohydrazide **2** [11]. Triazoles **3d–j** prepared for the first time are described in Table I. Triazoles **3a–c** [11] required for the synthesis of **5a–c** were also prepared. These were converted into 3-aryloxyalkyl-6-aryl-7*H*-*s*-triazolo[3,4-*b*][1,3,4]thiadiazines **5** in one step, by the reaction of **3** with phenacyl or 4-bromophenacyl bromides **4** in dry ethanol followed by

Table I. 4-Amino-3-aryloxyalkyl-5-mercapto-1,2,4-triazoles **3d–j**.

Compd.	R_1	R_2	R_3	R_4	mp °C	Yield (%)	Mol. formula [a]
3d	H	CH_3	H	Cl	153–54	65	$C_{10}H_{11}ClN_4OS$
3e	H	H	O–CH_2–O		219	64	$C_{10}H_{10}N_4O_3S$
3f	CH_3	H	H	H	139–42	65	$C_{10}H_{12}N_4OS$
3g	CH_3	H	H	Cl	153–55	63	$C_{10}H_{11}ClN_4OS$
3h	CH_3	Cl	H	Cl	135–36	65	$C_{10}H_{10}Cl_2N_4OS$
3i	CH_3	CH_3	H	Cl	115–16	60	$C_{11}H_{13}ClN_4OS$
3j	CH_3	H	O–CH_2–O		156–58	6	$C_{11}H_{12}N_4O_3S$

[a] All compounds were analyzed for C, H, N; the results obtained were within ± 0.4% of the theoretical values.

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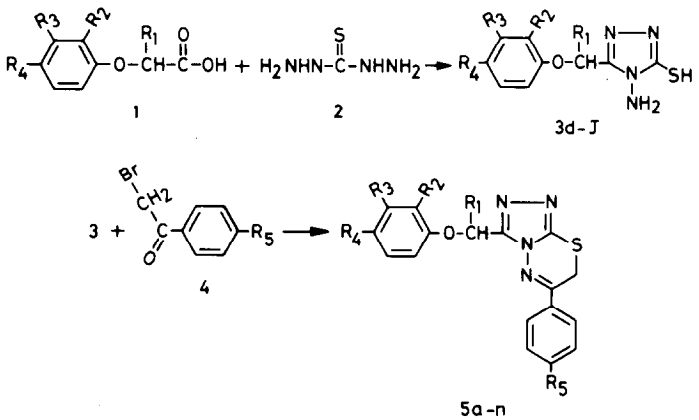
neutralization with ammonium hydroxide (Scheme 1). The structure of these compounds was confirmed by elemental analysis, IR, ^{1}H NMR and mass spectra. The synthesized compounds along with their analgesic and anti-inflammatory activities are described in Table II.



Scheme 1.

Results and Discussion

From the results summarized in Table II, it is apparent that all the compounds exhibited an interesting profile of analgesic activity, whereas few compounds showed mild to moderate anti-inflammatory activity. A few broad generalizations concerning the structure–activity relationships could be drawn regarding the compounds tested in the present study.

Compounds **5b** and **5e** having an aryloxymethyl substituent at the 3-position of the fused heterocycle and chloro and methylenedioxy groups, respectively, in the aryl ring, showed remarkable analgesic activities (83 and 67%). Similarly, compounds **5i** and **5l** having an aryloxyethyl substituent at the 3-position with chloro and methylenedioxy groups, respectively, in the aryl ring exhibited promising analgesic activity (73 and 80%) in comparison to aspirin (57%). However, compounds **5a** with phenoxymethyl and **5h** with phenoxyethyl substituents at the 3-position also exhibited analgesic activity (50 and 69% respectively).

It is inferred that, in both the phenoxymethyl and phenoxyethyl series, introduction of a bromine group into

Table II. 3-Aryloxyalkyl-6-aryl-*s*-triazolo[3,4-*b*][1,3,4]thiadiazines **5a–n**.

Compd.	R_1	R_2	R_3	R_4	R_5	mp °C	Yield %	Mol. formula[a]	Analgesic and anti-inflammatory actions[b]			
									n^c	% protection from pain	n^c	% inhibition of inflammation
5a	H	H	H	H	H	142	60	$C_{17}H_{14}N_4OS$	6	50.12 ± 2.25	3	10
5b	H	H	H	Cl	H	151	55	$C_{17}H_{13}ClN_4OS$	8	80.35 ± 3.88[d]	3	14
5c	H	Cl	H	Cl	H	146	56	$C_{17}H_{12}Cl_2N_4OS$	6	25.00 ± 6.85	3	9
5d	H	CH_3	H	Cl	H	149	54	$C_{18}H_{15}ClN_4OS$	6	36.00 ± 3.95	8	30.56 ± 3.85
5e	H	H	O–CH_2–O		H	136	52	$C_{18}H_{14}N_4O_3S$	8	67.07 ± 2.56[d]	3	8
5f	H	H	H	Cl	Br	157	56	$C_{17}H_{12}BrClN_4OS$	5	33.20 ± 2.82	3	7
5g	H	H	O–CH_2–O		Br	162	50	$C_{18}H_{13}BrN_4O_3S$	6	45.12 ± 6.54	3	7
5h	CH_3	H	H	H	H	180	60	$C_{18}H_{16}N_4OS$	8	69.39 ± 2.32[d]	8	20.68 ± 2.56
5i	CH_3	H	H	Cl	H	154	52	$C_{18}H_{15}ClN_4OS$	6	73.48 ± 3.05[d]	3	12
5j	CH_3	Cl	H	Cl	H	166	52	$C_{18}H_{14}Cl_2N_4OS$	6	43.31 ± 5.65	6	41.05 ± 3.25
5k	CH_3	CH_3	H	Cl	H	137	54	$C_{19}H_{17}ClN_4OS$	5	24.21 ± 8.35	6	42.45 ± 4.92
5l	CH_3	H	O–CH_2–O		H	142	52	$C_{19}H_{16}N_4O_3S$	10	80.34 ± 2.72[d]	3	9
5m	CH_3	H	H	Cl	Br	184	50	$C_{18}H_{14}BrClN_4OS$	6	33.02 ± 3.85	3	11
5n	CH_3	H	O–CH_2–O		Br	189	52	$C_{19}H_{15}BrN_4O_3S$	6	45.85 ± 2.10	3	13
Aspirin									10	57.35 ± 4.55[d]	–	–
Phenylbutazone									–	–	10	39.46 ± 3.22

[a]All compounds were analyzed for C, H, N; the maximum deviation observed from the theoretical values was ±0.4%.
[b]Dose: 100 mg/kg, *p.o.* n^c = number of animals used. [d] = $p < 0.01$

the phenyl ring at the 6-position of the fused heterocycle led to substantial reduction in the analgesic activity (**5b**→**5f**: 83→33%; **5e**→**5g**: 67→45%; **5i**→**5m**: 73→33%; **5l**→**5n**: 80→45%). Similarly, compounds **5d** and **5k** which have methyl groups in the phenoxy ring at the 3-position of the heterocycle had considerably decreased analgesic activities in comparison to their counterparts **5b** and **5i** (**5b**→**5d**: 83→36%; **5i**→**5k**: 73→24%). By contrast, incorporation of a methylenedioxy substituent into the aryloxyalkyl group produced a marginal increase in the analgesic activity (**5a**→**5e**: 50→67%; **5h**→**5l**: 69→80%).

In anti-inflammatory testing, compounds (**5j** and **5k**) showed anti-inflammatory activities (41 and 42%, respectively) comparable to the standard, phenylbutazone (39%), while others were less active (Table II).

Representative compounds **5e** and **5l** were evaluated for anti-fungal activities using nystatin as the standard. Compounds **5e** and **5l** showed inhibition zones (5 and 4 mm) against *Aspergillus flavous* and (4 and 3 mm) against *Penicillium tardum*, respectively, while nystatin's inhibition zones were 15 and 16 mm, respectively.

Experimental protocols

Chemistry

Melting points were determined on a Buchi capillary melting point apparatus and are uncorrected. IR spectra were recorded on a Perkin–Elmer 283B spectrophotometer in a potassium bromide pellet. The NMR spectra were determined on a Jeol FX90Q FT NMR spectrometer using tetramethylsilane as an internal standard. Mass spectra were recorded on a VG 7070H mass spectrometer at 70 eV. The purity of all the compounds was verified by thin–layer chromatography.

4-Amino-3-aryloxyalkyl-5-mercapto-1,2,4-triazoles **3** *(Table I)*
General procedure. A mixture of thiocarbohydrazide **2** (0.10 mol) and corresponding aryloxyalkyl carboxylic acid **1** (0.11 mol) was heated in an oil bath at 160–170°C for 2 h. The fused mass thus obtained was triturated with hot water to obtain the triazole. The product was recrystallized from methanol. Compound **3d** showed characteristic IR bands at 3300 (NH_2), 1620 (C=N), 1580 (aromatic) and 1245 (ether linkage). ^1H NMR ($CDCl_3$; **3d** δ: 6.90 (**br**, 1H, NH); 5.71 (*br*, 2H, NH_2); 3.60 (*s*, 2H, OCH_2); 2.36 (*s*, 3H, CH_3) and 7.20–7.71 (*m*, 3H, aromatic). MS: 270 (M^+), 142 ($M^+ - C_3H_4N_4S$), 129 ($M^+ - C_7H_6ClO$), 107 ($M^+ - C_3H_4ClN_4S$), 113 ($M^+ - C_7H_8ClNO$), 97 ($M^+ - C_7H_6ClOS$) and 85 ($M^+ - C_7H_8ClN_3O$).

*3(Aryloxyalkyl)-6-aryl-7*H-s-*triazolo[3,4-*b*][1,3,4]-thiadiazines* **5a–n** *(Table I)*
General procedure. A mixture of 4-amino-3-aryloxyalkyl-5-mercapto-1,2,4-triazole (0.02 mol) and phenacyl bromide or 4-bromophenacyl bromide (0.02 mol) in anhydrous ethanol (60 ml) was heated under reflux for 5 h, cooled to room temperature and then neutralized with ammonium hydroxide. The product thus obtained was recrystallized from ethanol. Compound **5a** in Table II showed characteristic IR bands at 1600 (C=N), 1230 (ether linkage), 2900, 2920 (alkyl)cm^{-1}. ^1H NMR ($CDCl_3$; **5a** δ: 7.35–7.85 (*m*, 5H, aromatic at 6-position); 7.01–7.25 (*m*, 5H, aromatic at 3-position); 5.19 (*s*, 2H, $O-CH_2$); 4.35 (*s*, 2H, CH_2). MS: 322 (M^+), 289 ($M^+ - SH$), 157 ($M^+ - (SH+C_8H_6NO)$), 229 ($M^+ - C_6H_5O$), 84 ($M^+ - C_6H_5O+C_8H_7N_3$), 219 ($M^+ - C_6H_5CN$), 103 ($M^+ - C_{10}H_9N_3SO$) and 118 ($M^+ - C_9H_6N_3OS$).

Biological activity

Compounds **5a–n** were screened for analgesic and anti-inflammatory activities. All test compounds were administered orally in 2% gum acacia suspension at a dose of 100 mg/kg. Aspirin and phenylbutazone were used, respectively, as the standards for analgesic and anti-inflammatory tests for comparison. Statistical analyses were made using Student's *t* test *versus* controls, as shown in Table II. Compounds **5e** and **5l** were also screened for anti-fungal activity.

Analgesic activity
A modified version of the acetic acid writhing test described by Koster *et al.* [12] was used. Results are given in Table II.

Anti-inflammatory (anti-edematous) activity
Carrageenin-induced rat paw edema [13] was used. The results are given in Table II.

Anti-fungal activity
The disc method [14] was followed using the fungi *Aspergillus flavus* and *Penicillium tardum* at a concentration of 10 mg/ml.

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