ELSEVIER

www.elsevier.nl/locate/farmac

Il Farmaco 55 (2000) 406–409

IL FARMACO

1,5-Benzodiazepine derivatives of 3-arylsydnones: synthesis and antimicrobial activity of 3-aryl-4-[2′-aryl-2′,4′,6′,7′-tetrahydro-(1′H)-1′,5′-benzodiazepine-4′-yl]sydnones

Jyoti R. Kavali, Bharati V. Badami *

Post-graduate Department of studies in Chemistry, Karnatak University, Dharwad 580 003, India

Received 1 September 1999; accepted 2 May 2000

Abstract

The α-β-unsaturated ketones of 3-arylsydnones (**Ia**–**y**) were treated with 1,2-phenylenediamine to obtain the 3-aryl-4-[2′-aryl-2′,4′,6′,7′-tetrahydro-(1′H)-1′,5′-benzodiazepine-4′-yl]sydnones (**IIa**–**y**) in high yield. All the new compounds synthesised were screened for antibacterial and antifungal activities. © 2000 Elsevier Science S.A. All rights reserved.

Keywords: Benzodiazepine derivatives; 3-Arylsydnones; Antimicrobial activity

1. Introduction

The synthesis and the pharmacological properties of 3-arylsydnones incorporated with a wide variety of heterocycles have been reported from this laboratory earlier [1–6]. As a part of this programme we have documented the use of the α-β-unsaturated ketones of 3-arylsydnones as useful precursors in the synthesis of the corresponding pyrazoline and indazoline derivatives [7,8]. The present work is directed to further the synthetic utility of these α-β-unsaturated ketones in the preparation of the 1,5-benzodiazepine derivatives and to explore their structure activity relationship (SAR). Recent reports have claimed the use of 1,5-benzodiazepines as antileukemic and antineoplastic agents [9], analgesic [10], antipsychotic agents [11], fungicides [12] and antimicrobial agents [13]. In view of these observations it was thought of interest to incorporate 1,5-benzodiazepine ring on 3-arylsydnone, in order to evaluate the biological properties.

2. Chemistry

We report herein the synthesis of 3-aryl-4-[2′-aryl-2′,4′,6′,7′-tetrahydro(1′H)-1′,5′-benzodiazepine-4′-yl]-sydnones (**IIa**–**y**, see Table 1), their spectral data and the antimicrobial properties (see Table 2).

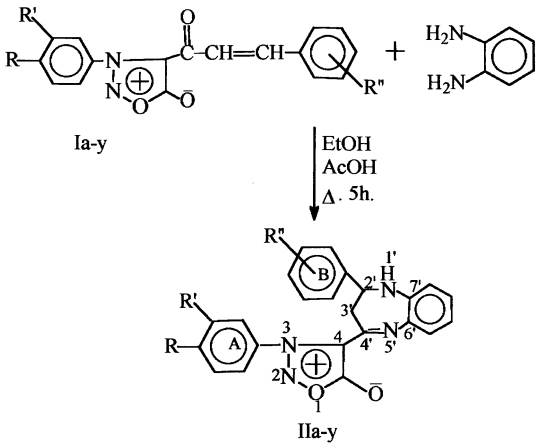
The target molecules were synthesised by a facile one step-condensation of 3-aryl-4-[3′-aryl-1′-oxo-2′-propen-1′-yl]sydnones (**Ia**–**y**) with 1,2-phenylenediamine in presence of acetic acid. The probable mechanism involves the Michael addition of one of the amino groups of 1,2-phenylenediamine to the activated olefin of compounds **Ia**–**y** in the initial step. This is followed by an in situ intramolecular nucleophilic attack by the other amino group resulting in the formation of the cyclocondensed products **IIa**–**y** (Scheme 1). The products were obtained as bright red crystals from the yellow starting compounds. This bathochromic shift is due to the conjugation of the benzodiazepine ring with the polar sydnone ring. Compounds **Ia**–**y** were prepared from 4-acetyl-3-arylsydnones following a method reported in the literature [8].

2.1. Spectral data

UV spectra of compounds **IIa**–**y** showed a considerable bathochromic shift due to the π–π* (λ_{max} 452, 450

* Corresponding author. Tel.: +91-836-771275.
E-mail address: bbadami@usa.net (B.V. Badami).

PII: S0014-827X(00)00061-6



Scheme 1.

nm) as compared to that of compounds **Ia**–**y** (λ_{max} 371–5, 335 nm). The IR spectra of all these compounds showed a band at 1720 cm^{-1} characteristic of sydnone $\nu_{C=O}$ and a band at 3363 cm^{-1} for ν_{NH}. The characteristic signals observed for ^{1}H-NMR (300 MHz) for all these compounds are two doublets at δ 3.3–3.4 for C'_3 methylene protons (diastereotopic) due to vicinal coupling ($J = 15$ Hz), a multiplet for the C'_2 methine proton (coupled with 3′CH_2 and NH) at δ 5.2–5.3 and a broad signal at δ 4.1 (D_2O exchanged) for NH proton. The aromatic protons appeared as multiplets at δ 6.55–7.40 ppm.

2.2. Biological evaluation (antimicrobial activity)

All these compounds were screened for their in vitro antimicrobial activity against two bacteria viz, *E. coli* and *C. bacillus* and two fungal cultures viz, *A. candida* and *R. bataticola*. The reference drugs used were Norfloxacin and Griseofulvin, respectively. The tests were carried out with the title compounds and the reference drugs, under identical conditions by cup-plate method with 20 μg of the substance in 0.1 ml of dimethylformamide. The total area of inhibition was calculated by the zone of inhibition, in comparison with the reference drug, as follows:

Relative % inhibition $= 100(X - Y)/(Z - Y)$

$X =$ total area of inhibition in test plate

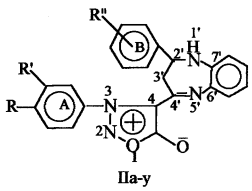
$Y =$ total area of inhibition in solvent (DMF) plate

$Z =$ total area of inhibition in reference plate.

3. Results and discussion

The antibacterial screening results have shown that the halogen, methyl and nitro substituted compounds exhibit, in general, growth inhibitory activity more relevant than that of the reference compounds; this activity varies with the substitutions on phenyl ring A and B.

Table 1



3-Aryl-4-[2′-aryl-2′,4′,6′,7′-tetrahydro-(1′H)-1′,5′-benzodiazepine-4′-yl]-sydnones **IIa**–**y**

Comp.	R	R′	R″	Yield (%)	M.P. (°C)
IIa	H	H	H	60	151–152
IIb	Br	H	H	66	210–211
IIc	CH_3	H	H	63	191–192
IId	Cl	H	H	70	194–195
IIe	CH_3	H	Cl (o)	68	225–226
IIf	OCH_3	H	H	70	171–172
IIg	H	H	Cl (o)	50	181–182
IIh	H	H	Cl (p)	65	165–166
IIi	H	H	OCH_3 (p)	55	191–192
IIj	H	H	NO_2 (p)	65	281–282
IIk	CH_3	H	CH_3 (p)	60	230–231
IIl	OCH_3	H	NO_2 (o)	65	212–213
IIm	CH_3	H	Cl (p)	75	191–192
IIn	CH_3	H	NO_2 (o)	72	200–201
IIo	Br	H	Cl (p)	75	199–200
IIp	Cl	H	CH_3 (p)	65	175–176
IIq	Cl	H	Cl (o)	62	205–206
IIr	Cl	H	Cl (p)	68	198–200
IIs	Cl	H	NO_2 (p)	55	170–171
IIt	OCH_3	H	Cl (o)	55	215–216
IIu	OCH_3	H	Cl (p)	80	182–183
IIv	CH_3	CH_3	H	60	148–149
IIw	CH_3	CH_3	Cl (p)	70	162–163
IIx	CH_3	Cl	H	62	174–175
IIy	CH_3	Cl	Cl (p)	60	164–165

It is worth noting that compound **IIh**, with a chloro on the *para* position, showed growth inhibitory activity 3.5 times higher than Norfloxacin against *E. coli*, but lower activity against *C. bacillus*, while its *ortho* isomer **IIg** is inactive against both strains. This is an example which shows how the biological properties are influenced by even minor structural modifications. Some of these compounds (**IIa**, **IId**, **IIm**, **IIn**, **IIo**, and **IIu**) are as active as Norfloxacin against *E. coli* only. All the other derivatives show from weak to moderate activity. The chloro substituted compounds, (**IId**, **IIn**, **IIr** and **IIs**) are from two to three times more active than Griseofulvin against both the strains. Additional chloro or methyl groups do not cause any variation in the activity. Most of the other compounds are as active as the reference compound against both the strains. The methyl and nitro substitution (**IIc** and **IIj**) have shown highest activity amongst all the compounds against both fungi. In general these compounds are found to possess more antifungal than antibacterial activity.

Table 2
Results of antibacterial and antifungal activity [a]

Comp.	*E. coli* (gram −ve)		*C. bacillus* (gram +ve)		*A. candida*		*R. bataticola*	
	Zone of inhibition (mm)	Relative inhibition (%)	Zone of inhibition (mm)	Relative inhibition (%)	Zone of inhibition (mm)	Relative inhibition (%)	Zone of inhibition (mm)	Relative inhibition (%)
IIa	95.07	99.99	176.78	5.44	380.28	183.57	95.07	100.00
IIb	78.57	47.49	176.78	5.44	113.14	209.52	78.57	0.00
IIc	78.57	47.49	154.00	0.00	78.57	0.00	78.57	0.00
IId	95.07	99.99	707.14	132.08	113.14	209.52	132.78	328.57
IIe	63.64	0.000	176.78	5.44	78.57	0.000	78.57	0.00
IIf	78.57	47.49	176.78	5.44	95.07	100.00	78.57	0.00
IIg	63.64	0.000	176.78	5.44	78.57	0.000	78.57	0.00
IIh	176.78	359.99	314.28	38.27	113.14	209.52	113.14	209.52
IIi	78.57	47.49	346.50	45.96	132.78	328.57	95.07	100.00
IIj	78.57	47.49	491.07	80.48	132.78	328.57	113.14	209.52
IIk	78.57	47.49	201.14	11.25	78.57	0.000	78.57	0.00
IIl	78.57	47.49	176.78	5.44	113.14	209.52	78.57	0.00
IIm	95.07	99.99	176.78	5.44	113.14	209.52	78.57	0.00
IIn	95.07	99.99	491.07	80.48	132.78	328.57	132.78	328.57
IIo	95.07	99.99	491.07	80.48	95.07	100.00	95.05	100.00
IIp	113.14	157.49	314.28	38.27	113.14	209.52	95.07	100.00
IIq	78.57	47.49	201.14	11.25	78.57	0.000	78.57	0.00
IIr	78.57	47.49	227.07	17.44	113.14	209.52	132.78	328.57
IIs	78.57	47.49	154.00	0.00	95.07	100.00	132.78	328.57
IIt	78.57	47.49	154.00	0.00	78.57	0.000	78.57	0.00
IIu	95.07	99.99	176.78	5.44	95.07	100.00	95.07	100.00
IIv	78.57	47.49	176.78	5.44	78.57	0.000	78.57	0.00
IIw	78.57	47.49	227.07	17.44	95.07	100.00	113.14	209.52
IIx	78.57	47.49	154.00	0.00	95.07	100.00	95.07	100.00
IIy	78.57	47.49	227.07	17.44	95.07	100.00	78.57	0.00

[a] Relative inhibition of reference drugs is taken as 100%.

4. Experimental

TLC was performed on preactivated (110°) silica gel plates using benzene and alcohol (1:3) as eluent. The m.p.s are uncorrected. The spectra were recorded on IR NICOLET-IMPACT-410 FTIR. ^{1}H-NMR were recorded on BRUKER-AC-300F 300 MHz NMR spectrometer in $CDCl_3$, with TMS as internal standard. Elemental analysis results are within 0–4% of the calculated values.

*4.1. Synthesis of 3-aryl-4-[2′-aryl-2′,4′,6′,7′-tetrahydro-(1′H)-1′,5′-benzodiazepine)-4′-yl]sydnones (**IIa–y**), general procedure*

3-Aryl-4(3′-aryl-1′-oxo-2′-propen-1′-yl)sydnones (**Ia–y**) (3.40 g, 0.01 mol) and 1,2-phenylenediamine (1.08 g, 0.01 mol) were taken in absolute alcohol (20 ml) containing acetic acid (1 ml). The mixture was refluxed on a water-bath for 5 h. The solvent was evaporated to obtain the title compounds. The compounds on further purification by crystallisation from ethanol gave red crystals (nitro substituted compounds were yellow). Some physical properties are reported in Table 1.

Acknowledgements

Authors are thankful to Punjab University, Chandigarh for spectral facilities.

References

[1] K.G. Upadhya, B.V. Badami, G.S. Puranik, Synthesis and antimicrobial activity of 3-substituted-4-(4-thiazolyl)sydnones, Arch. Pharm. 313 (1980) 684–688.

[2] R.K. Tikare, K.G. Upadhya, B.V. Badami, G.S. Puranik, Synthesis and biological activity of 4-substituted-3-arylsydnones, Indian J. Chem. 23B (1984) 798–800.

[3] C.V. Yelamaggad, U.S. Hiremath, B.V. Badami, Synthesis and evaluation of 4-[3-methyl/aryl-7H-s-triazol(3,4-b)(1,34)-thiadiazin-6-yl]-3-arylsydnones, Indian J. Chem. 33B (1994) 707–709.

[4] B.M. Patil, B.V. Badami, G.S. Puranik, Synthesis and Analgesic evaluation of 3-aryl-4-(4-formyl-1-phenylpyrazol-3-yl)sydnones, Indian Drug 32 (10) (1995) 439–441.

[5] S.G. Mallur, B.V. Badami, Heteroarylmercapto derivatives of 3-aryl sydnones Part I, Indian J. Het. Chem. 8 (1998) 159–160.

[6] S.G. Mallur, B.V. Badami, Bridgehead nitrogen heterocycles containing spirolinkage on 3-arylsydnones, Indian J. Het. Chem. 8 (1999) 343–344.

[7] D.B. Dambal, P.P. Pattanashetti, R.K. Tikare, B.V. Badami, G.S. Puranik, Reactions of 3-(*p*-acetylphenyl)sydnones Part-III, Indian J. Chem. 23B (1984) 186–190.

[8] C.K. Hosamani, B.V. Badami, Michael addition of ethylacetoacetate to the α,β-unsaturated ketones of 3-arylsydnones, Indian J. Het. Chem. 7 (1998) 245–248.

[9] W. Werner, W. Gutsche, J. Baungart, Preparation of benzopyrano[4,3-b]-1,5-benzodiazepines as drugs and drug intermediates, Chem. Abstr. 112 (1990) 55925s.

[10] (a) M. Di Brassio, G. Roma, G.C. Grossi, M. Ghima, E. Mereto, 1,5-Benzodiazepines VIII, Eur. J. Med. Chem. 25(8) (1990) 681–687. (b) M. Di Brassio, G. Roma, G.C. Grossi, M. Ghima, E. Mereto, Novel 4H-[1,2,4] triazolo [4,3-a] 1,5-benzodiazepine derivatives with analgesic or antiinflammatory activity, Chem. Abstr. 114 (1991) 164175j.

[11] D.T. Kavita, G. Achaiah, V.M. Reddy, Synthesis of 6-alkyl/aryl-5,11-dihydro-9-nitro[1]benzopyrano[2,3-b][1,5]benzodiazepin-1,3-ones as possible antipsychotic agents, J. Indian Chem. Soc. 65 (8) (1988) 567–570.

[12] J. Deleny, James, Cook Ewell Russel, 1,3-Dihydro-4-phenyl-2H-1,5-benzodiazepin-2-ones their preparation and their use as agrochemical fungicides, Chem. Abstr. 117 (1992) 151023v.

[13] Hargare D. Karl, T.A. Kelly et al., 2-Heteroaryl-5, 11-dihydro-6H-dipyrido[3,2-b:2,3-e][1,4]diazepines and their use in the prevention or treatment of HIV infection, Chem. Abstr. 124 (1996) 55993k.