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Pharmaceutica Acta Helvetiae 69 (1994) 163–169

PHARMACEUTICA ACTA HELVETIAE

Synthesis and analgesic properties of 5-acyl-arylhydrazone 1-H pyrazolo [3,4-b] pyridine derivatives ☆

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Received 14 July 1994; accepted 12 August 1994

Abstract

A series of 5-acyl-arylhydrazone 1-H pyrazolo [3,4-b] pyridine derivatives (**1**), planned by applying classical ring isosterism, were synthesized in order to evaluate the structure-activity relationship (SAR), especially the participation of the structural acyl-arylhydrazone subunit in the analgesia. The synthetic route used produced the derivatives **1** in ~ 40% overall yield, using **9** as key intermediate. The results obtained from this study showed that in general the compounds of this series present a powerful analgesic activity in the test of abdominal contortions induced by acetic acid i.p. in albino mice, indicating the participation of the acyl-arylhydrazone moiety, as well the relevance of the substituent of the aryl ring, in the activity.

Keywords: Analgesic properties; Medicinal chemistry; Pyrazole [3,4-b] pyridine

1. Introduction

Several nitrogen heterocyclic compounds containing the acylhydrazone moiety, such as the pyrazole derivative **2**, have shown an important effect in the biotransformation of arachidonic acid metabolites by inhibition of the cyclooxygenase and 5-lipooxygenase enzymes (Tihany et al., 1984). Due to this dual activity these compounds are able to reduce the eicosanoid bioformation and consequently the leukocyte migration in inflammatory exudates (Higs et al., 1980; Sincholle et al., 1987). The participation of several autacoids, including histamine, bradykinin, serotonin, prostaglandin E_2 (PGE_2), leukotrienes and other agents, as mediators of pain after noxious stimuli can explain the analgesic properties of arachidonic acid enzyme inhibitors, relieving mild to moderate pain (Vane, 1971).

As part of a research program aiming at synthesis and pharmacological evaluation of new isosteres of arachidonic acid cascade enzyme inhibitors (Matheus et al., 1991; Silveira et al., 1991, 1993; Fraga and Barreiro, 1992; Freitas and Barreiro, 1992; de Lima and Barreiro, 1992; Silva and Barreiro, 1993), we described in previous work the activity of a series of 4-acyl-arylhydrazone pyrazole derivatives (**3**) which showed a potent analgesic activity in vivo (Matheus et al., 1991). These results conduct us to explore the search of new structurally related compounds, which could show the same analgesic activity. With this rational basis in mind we disclose in this paper the synthesis and analgesic activity of a series of 5-acyl-arylhydrazone 1-H pyrazolo [3,4-b] pyridine derivatives (**1**) (Dias, 1992). The general structure of **1** was designed upon

☆ This paper is contribution no. 03 from LASSBio, UFRJ.

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SSDI 0031-6865(94)00035-2

the bioisosteric relationship between pyrazole and pyrazolo pyridine rings (Barreiro, 1991) and assuming that the acylhydrazone group would be an important pharmacophore to analgesic activity in these series.

2. Experimental procedures

2.1. Chemistry

Infrared (IR) spectra were obtained with a Perkin-Elmer 1600 spectrometer by using potassium bromide plates. The mass spectra were obtained with a GC/VG Micromass 12 at 7 eV. Nuclear magnetic resonance (^{1}H-NMR and ^{13}C-NMR) spectra were determined in dimethylsulfoxide (DMSO) containing ca. 1% TMS as an internal standard with a Varian T-60 at 60 MHz, AC 200 Brucker and VXR 300 Varian and GEMINI 300 Varian spectrophotometers. Splitting patterns are as follows: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; b, broad.

The progress of all reactions was monitored by tlc, which was performed on 2.0 cm × 6.0 cm alumin sheets precoated with silica gel 60 (HF-254, Merck) to a thickness of 0.25 mm. The developed chromatograms were viewed under ultraviolet light (254–265 nm). Solvents used in the reactions were generally distilled before use.

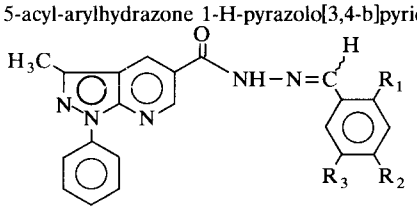
Ethyl-(1-phenyl-3-methyl pyrazolo [3,4-b]pyridinyl)-5-carboxylate (8)

To a mixture of 3 g (6.4 mM) of the chloro derivative (**7**), 0.53 g (6.4 mM) of anhydrous sodium acetate and glacial acetic acid, maintained under stirring and warming at 70°C until complete dissolution, was added 0.175 g of 10% Pd/C to a reactor connected to a Parr hydrogenator, at 40 psi and 55–70°C. The reaction mixture was maintained under hydrogen atmosphere for 4 h. The reaction course was followed by the pressure fallen, which was quick in the first 30 min and slow after this time. Product isolation was achieved by simple filtration and the solvent eliminated producing a precipitate with further addition of cool water. This precipitate was filtered and dried in a dessicator, showed a m.p. 110°C with a yield of 95%. IR (KBr): (C = O) 1711, (C–O) 1262 cm^{-1}; ^{1}H-NMR (300 MHz) DMSO-d$_6$: 9.08 (d, J = 1.8 Hz, 1H, H-6), 8.78 (d, J = 1.8 Hz, 1H, H-4), 8.21 (dd, J = 7.5 Hz, 2H, H-1′), 7.54 (dd, J = 7.5 Hz, 2H, H-2′), 7.33 (dd, J = 7.3 Hz, 1H, H-3′), 4.40 (q, 2H, **–CH$_2$–**CH$_3$), 2.63 (s, 3H, CH$_3$), 1.38 ppm (t, 3H, **CH$_3$–**CH$_2$–); ^{13}C-NMR (50 MHz) DMSO-d6: 164.51 (C = O), 151.0 (C-6), 144.37 (C-8), 138.52 (C-1′), 132.1 (C-4), 129.0 (C-3 and C-3′), 125.76 (C-4′), 120.04 (C-2′), 119.16 (C-5), 115.91 (C-9), 60.96 (–CH$_2$), 14.08 (**CH$_3$–**CH$_2$–), 11.96 ppm (CH$_3$).

5-acyl-(1-phenyl-3-methyl pyrazolo [3,4-b] pyridinyl) hydrazine (9)

An ethanolic solution of 4 g (14 mM) of **8** in 50 ml of ethanol was heated under stirring until complete dissolution. Then 14 ml of hydrazine hydrate was added. The reaction mixture was still stirred at reflux for 3 h. At the end of reaction (observed by tlc) the product **9**, 75%, was isolated by concentration of reaction mixture under reduced pressure and cold water addition to furnish the product as a yellow light solid,

Table 1
5-acyl-arylhydrazone 1-H-pyrazolo[3,4-b]pyridine (**1**)



Compound	Substituents			Molecular formula	Yield (%)	Molecular weight	m.p. (°C)
	R_1	R_2	R_3				
1a	H	H	H	$C_{21}H_{17}N_5$	90	355	230
1b	CF_3	H	H	$C_{22}H_{16}N_5OF_3$	92	423	204
1c	H	CF_3	H	$C_{22}H_{16}N_5OF_3$	90	423	260
1d	H	CN	H	$C_{22}H_{16}N_6O$	96	380	281
1e	NO_2	H	H	$C_{21}H_{16}N_6O_3$	90	400	245
1f	H	NO_2	H	$C_{21}H_{16}N_6O_3$	92	400	295
1g	H	F	H	$C_{21}H_{16}N_5OF$	90	373	235
1h	H	O–CH_2–O		$C_{22}H_{17}N_5O_3$	96	399	249
1i	NO_2	O–CH_2–O		$C_{22}H_{16}N_6O_5$	95	444	270

m.p. 219–221°C. IR (KBr): (NH) 3273, (C = O) 1607 cm^{-1}; ^{1}H-NMR (300 MHz) DMSO-d_6: 10.10 (b, NH), 9.12 (s, 1H, H-6), 8.82 (s, 1H, H-4), 8.31 (dd, J = 7.9 Hz, 2H, H-1'), 7.63 (dd, J = 7.9 and 7.6 Hz, 2H, H-2'), 7.41 (dd, J = 7.6 Hz, 1H, H-3'), 2.70 ppm (s, 3H, CH_3); ^{13}C-NMR (75 MHz) DMSO-d_6: 164.42 (C = O), 150.62 (C-6), 148.40 (C-8), 143.99 (C-1'), 138.79 (C-4), 129.70 (C-3), 129.12 (C-3'), 125.70 (C-4'), 122.73 (C-5), 120.11 (C-2'), 115.98 (C-9), 121.31 ppm (CH_3).

*General procedure for obtaining 5-acyl-(1-phenyl-3-methyl pyrazolo [3,4-b] pyridinyl) aryl hydrazones (**1a–1i**)*

To a solution of 0.21 g (78 mM) of hydrazine derivative (**9**) in absolute ethanol sufficient to complete dissolution of the reaction mixture was added benzaldehyde derivative (78 mM) in the presence of two drops of chloridic acid as catalyst. The end of reaction was observed by tlc, and the hydrazones (**1**) were isolated by concentration of the reaction mixture under reduced pressure and addition of cold water to furnish the desired product as a colored precipate in ~ 90% yield (Table 1).

2.2. Pharmacology

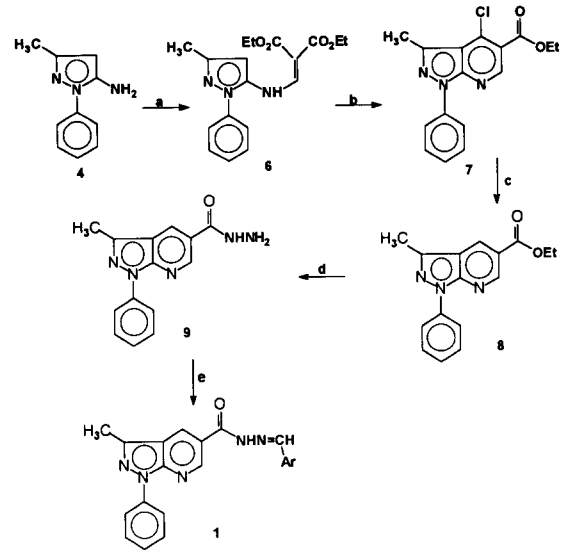
Analgesic activity

The analgesic activity was determined in vivo using the abdominal constriction test induced by acetic acid 0.6% (0.1 ml/10 g) in albino mice (Whittle, 1964) (ca. 20 g); dipyrone (100 μM) was used as standard. The solution of acetic acid was administered i.p. and the number of constrictions registered during 30 min (control). All compounds were administered p.o. in saline (dipyrone) or in propylene glycol (**1a–1i**) at a dose of 33 mg/kg (0.1 ml/20 g) 1 h before injection of acetic acid. The results are expressed as mean ± standard error of the mean for n number of animals. The inhibitory effect was calculated as percent of the control. The data were analyzed statistically by Student t-test, with the level of significance set at $P < 0.05$.

3. Results and discussion

3.1. Chemistry

Among the several possible synthetic approaches to derivatives **1**, we decided to use the 5-acyl-(1-phenyl-3-methyl pyrazolo [3,4-b] pyridinyl) hydrazine (**9**) as a key intermediate to the desired compounds **1**. Once using simple functional group interconversion, i.e. CONHNH$_2$ → CONHN = CHAr, the target compounds could be prepared by simple acidic condensation with the appropriate aldehydes. The compound **9** could be prepared in high overall yield by the synthetic sequence shown in Scheme 1, by using a nucleophilic substitution reaction of hydrazine hydrate (Khan and Freitas, 1983) on ethyl-(1-phenyl-3-methyl pyrazolo [3,4-b] pyridinyl) 5-carboxylate (**8**). Starting from 1-phenyl-3-methyl-5-amino pyrazole (**4**) (Bare et al., 1989) and diethyl ethoxymethylene malonate (**5**) by thermal condensation produced the enamine (**6**). Subsequent treatment of **6** with phosphorus oxychloride at reflux overnight furnished directly the 4-chloroester (**7**) (Forbes et al., 1990) in 80% yield. The next step in the planned synthetic route would be to submit the functionalized heterocyclic derivative **7** to a dehalogenation step by using hydrolysis conditions (Freifelder, 1971). After using several experimental conditions with 10% Pd/C (Bare et al., 1989; Murray et al., 1990) as catalyst in this reaction, we were finally able to obtain the heterocyclic ester **8** in appropriate yield by performing this hydrogenolisis step in a Parr reactor under 40 psi pressure at 55–70°C. These unusual hard conditions to this catalytic hydrogenation reaction could be explained by the presence of a C-3 methyl group. In fact, the compound 4-chloro-1-ethyl-6-methyl-1H-pyrazolo [3,4-b] pyridine-5-carboxylic acid ethyl ester (**10**) described by Bare et al. (1989), where this methyl group is absent, produced the dehalogenated product **8** in compatable yield by using standard conditions. The



Scheme 1. Synthesis of **1** from **4**. (a) **5**, reflux, 3h (75%); (b) $POCl_3$, reflux, overnight (80%); (c) 10% Pd/C, AcONa, 40 psi, 55–70°C, 4h (95%); (d) $NH_2NH_2 \cdot H_2O$, reflux, 3 h (75%); (e) ethanol, aromatic aldehyde, HCl, reflux (~ 90%).

Table 2
^{1}H nuclear magnetic resonance spectra at 300 MHz of the compounds **1** (J in Hz) [a]

	Compound								
	1a	1b	1c	1d	1e	1f	1g	1h	1i
NH	12.1; b	12.5; b	12.3;b	12.0; b	12.3; b	12.2; b	12.0; b	12.0; b	12.2; b
H-6	9.1; s	9.2; s	9.2; s	9.2; d	9.1; s	9.2; d	9.1; s	9.2; d;	9.2; s
H-4	8.9; s	9.0; s	8.9; s	8.9; d	8.8; s	9.0; d	8.8; s	8.9; d; J = 1.7	9.0; s
CH-Ar	8.5; s	8.9; s	8.6; s	8.6; s	8.8; s	8.7; s	8.4; s	8.4; s	9.0; s
H-2′	8.2; dd J = 8.0	8.3; dd J = 7.9	8.3;dd J = 7.9	8.3; dd J = 7.8	8.2; dd J = 8.2	8.1; dd J = 8.2	8.2; dd J = 7.7	8.3; dd; J = 7.8	8.4; dd J = 8.1
H-3′	7.6; dd J = 8.0	7.7; dd J = 7.9	7.6;dd J = 7.9 7.8	7.6; dd J = 7.8 8.0	7.5; dd; J = 8.2 7.6	7.7; dd J = 8.2 7.5	7.3; dd J = 7.7 8.3	7.6; dd J = 7.8 8.0	7.7; dd J = 8.1 7.0
H-4′	7.3; dd J = 9.0	7.4; dd; J = 7.6	7.4; dd; J = 7.6	7.4; dd; J = 8.0	7.3; dd; J = 7.6	7.4; dd; J = 7.5	7.3; dd; J = 8.3	7.0; dd; J = 8.0	7.4; dd J = 7.0
H-2″	7.5; dd J = 5.0	–	7.8; d; J = 8.0	8.0; d; J = 8.2	–	8.3; d; J = 9.0	7.8; d; J = 7.8	7.2; d; J = 7.5	–
H-3″	7.8; dd J = 5.0	8.3; dd J = 7.9	8.0; d J = 8.0	8.0; d; J = 8.2	8.1; dd J = 7.3	8.4; d; J = 9.0	7.5; d; J = 7.8	7.4; d; J = 7.5	7.75; s
H-4″	7.8; dd J = 9.0	7.9; m	–	–	7.6; ddd; J = 7.8;7.3	–	–	–	–
H-5″	–	7.9; m	–	–	7.8; ddd; J = 8.0;7.8	–	–	–	–
H-6″	–	7.7; d	–	–	8.0; dd; J = 8.0	–	–	7.4; s	7.6; s
CH_3	2.7; s	2.8; s	2.7; s	2.8; s	2.6; s	2.8; s	2.6; s	2.7; s	2.8; s
Others	–	–	–	–	–	–	–	6.2; 0-CH_2-0	6.4; s; 0-CH_2-0

[a] Ca. 30 mg of compound in 0.7 ml of DMSO-d_6.

chloro-elimination in the product **7** was proved by analyses of the ^{1}H-NMR spectrum, which shows a signal at δ 8.78ppm (J = 1.8 Hz) indicating the presence of a C-4 hydrogen atom.

Finally the key intermediate (**9**) was obtained by further treatment of an ethanolic solution of **8** with hydrazine hydrate at reflux. The desired compound **9** was obtained as a light-yellow solid in 75% yield.

Subsequent treatment of acylhydrazine (**9**) with the corresponding aromatic aldehydes in ethanol, using chloridic acid as catalyst, produced the desired acylarylhydrazone derivatives (**1**) (Dias, 1992) (Table 1) in ca. 90% yield.

The choice of the substituent pattern in the aldehyde moiety was defined in order to introduce a significant difference in the lipophilic character of these derivatives, permitting a study of SAR.

During the structural determination of these compounds we were able to detect that the acylhydrazone form (**A**) predominates over the enidrazine form (**B**) (Szileigyl et al., 1984) (Fig. 1) as shown by the analysis of infrared spectra indicating the presence of a strong absorption bond at ν 3.200 cm^{-1} attributed to a –NH group. The ^{1}H- and ^{13}C-NMR spectra showed signals at δ 8.5–9.0 and 144.2–148.5 ppm, respectively, attributed to methynic group (**CH** = Ar) (Lynch et al., 1988) (Tables 2 and 3). These data permit to conclude that form **A** is the predominant tautomer in this class

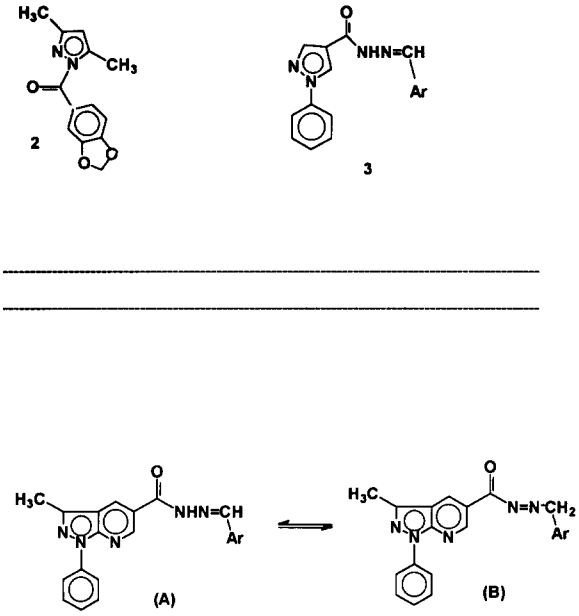


Fig. 1. Possible tautomeric forms of compound 1.

of hydrazones derivatives. Unfortunately, with the spectroscopic methods used, we were not able to identify the presence of both possible isomeric forms (E/Z) of the hydrazone unit, since the characteristic doublet signal in the ^{1}H- and ^{13}C-NMR spectra could not be observed, suggesting the existence of only a single

Table 3
^{13}C nuclear magnetic spectra at 75 MHz of the compounds **1** [a]

	Compounds								
	1a	**1b**	**1c**	**1d**	**1e**	**1f**	**1g**	**1h**	**1i**
C-3	130.6	130.6	130.5	130.1	130.8	130.8	130.6	130.4	130.3
C-3a	116.0	115.8	115.9	115.4	115.9	115.6	115.9	115.9	115.4
C-4	138.9	138.7	138.7	138.3	138.8	138.6	138.8	138.8	138.4
C-5	123.0	122.5	122.5	122.4	122.4	122.6	122.9	123.5	122.3
C-6	150.9	150.9	150.7	150.4	150.9	150.6	150.8	150.8	151.2
C-7a	149.3	149.2	149.1	148.7	149.4	148.9	149.2	149.2	148.9
CH_3	12.3	12.3	12.3	11.6	12.3	11.9	12.3	12.2	11.7
C = O	161.7	161.8	161.7		161.9		161.7	161.4	
CH-Ar	148.1	144.2	146.1	144.9	148.2	147.8	146.9	148.0	148.6
C-1′	144.4	142.8	144.2	143.5	144.4	143.9	144.3	144.2	143.7
C-2′	120.3	120.2	120.2	119.9	120.3	120.2	120.3	120.2	119.9
C-3′	129.0	129.1	129.1	128.3	129.2	129.0	129.1	129.2	128.6
C-4′	126.0	125.8	125.7	125.4	125.9	127.8	125.9	125.8	125.3
C-1″	134.3	132.0	138.1	138.2	128.7	140.2	129.5	128.6	148.6
C-2″	127.3	125.9	127.7	127.0	143.2	128.5	129.2	122.9	142.8
C-3″	129.3	126.9	127.7	131.9	128.0	123.6	116.1	108.5	104.4
C-4″	130.3	130.1	125.8	111.6	130 7	149.3	160.5	149.2	148.9
C-5″		132.8			133.8			147.8	150.6
C-6″		126.9			124.7			105.2	105.0
Other		125.9 (CF_3)	125.8 (CF_3)	117.8 (CN)				101.6 (OCH_2O)	103.3 (OCH_2O)

[a] Ca. 30 mg of compound in 0.7 ml of DMSO-d_6.

Table 4
In vivo effect of acyl-arylhydrazones derivatives (**1a–1i**) and dipyrone in the inhibition of abdominal constrictions induced by acetic acid (0.6%, i.p.) in mice

Compound	Concentration (μM)	n [a]	Contortion number	Inhibition (%)	Relative activity [b]
Control		62	93 ± 4.5		
Propylene glycol		21	90 ± 9.0	3.2	
Dipyrone	100	19	41 ± 8.5 *	55.9	1.0
1a	93	10	45 ± 6.6 *	51.6	0.95
1b	78	09	67 ± 12.5 *	27.9	0.61
1c	78	07	95 ± 10.6 *	−2.3	−0.05
1d	86	10	63 ± 9.4 *	32.2	0.62
1e	84	09	57 ± 7.7 *	38.7	0.77
1f	84	08	53 ± 8.8 *	43.0	0.86
1g	88	10	38 ± 4.3 *	59.1	1.14
1h	83	09	36 ± 8.3 *	61.2	1.25
1i	74	08	43 ± 3.7 *	53.7	1.23

[a] n = number of animals.
[b] The value of relative activity was obtained by comparison with the dipyrone attribute (activity equal to 1.0).
* $P < 0.05$.

diastereoisomere. These findings seem to indicate that in the condensation step between the acylhydrazide **9** with the different aldehydes a thermodynamic control was operating in favor of one diastereoisomeric product (Rodrigues et al., 1993).

Recent results using molecular modeling techniques from this laboratory with a similar series of compounds having the hydrazone moiety (**3**) show a small difference (ca. 3 kcal/mol) favoring the (Z)-isomer (Rodrigues et al., 1993).

3.2. Pharmacology

The evaluation of analgesic properties of these new 5-acyl-arylhydrazone pyrazolo [3,4-b] pyridine compounds (**1**) was performed using the induced abdominal constriction test. The results are shown in Table 4, expressed in molar ratio (Miranda et al., 1993), and indicate that the **1a** and **1g–1i** compounds were the most potent in this series, presenting an analgesic action superior to that shown by dipyrone (used as standard) at higher concentrations (Table 4). These results also suggest a possible action of these compounds in the arachidonic acid metabolism and invigorate the fact that the acylhydrazone moiety could be a possible pharmacophore for the analgesic activity (Ferreira et al., 1973) as previously observed in the 4-acyl-arylhydrazone pyrazole series (**3**) (Matheus et al., 1991).

To understand the eventual factor determining the nature of the substituent in the observed analgesic activity we performed a preliminary QSAR study. The investigation of the correlation between the activity showed by compounds **1** and the stereoelectronics and lipophilic parameters provided 44 equations. The best 10 equations were related to the electronic (σ) and lipophilic (π) parameters, involving parabolical correlations (π^2) (Dias et al., 1993). So the analgesic activity of compounds **1a**, **1c**, **1d**, **1f–1i** depends on substituents in para-position with π values approaching zero, as in the H (**1a**) and OCH_2O (**1h**, **1i**) moiety, as shown by the best equation (Eq. 1) (Dias et al., 1993). These analyses were carried out using the QSAR-PC:PAR program (Coburn, 1987).

$$\text{Analgesic activity} = -1.53(\pm 0.18)\ \pi^2 X + 1.12(\pm 0.06) \quad (1)$$

Number of compounds (n) = 7 (**1a,1c,1d,1f,1g,1h,1i**); standard error regression (s) = 0.13; multiple correlation coefficient (r) = 0.97; reliability test (F) = 73,31.

In conclusion, the synthetic methodology used in this work was shown to be efficient in obtaining these new pyrazolo [3,4-b] pyridine derivatives (**1a–1i**) in high yields. The pharmacological results confirm the anticipated analgesic activity in the model adopted, and the preliminary results of the QSAR study seem to suggest that the analgesic activity of series of heterocyclic compounds depends on the lipophilic factors of the substituents of aryl moiety in the hydrazone residue.

Acknowledgments

This work was supported by grants from the CNPq-Br (50.0833/91.5), International Foundation for Science – Sw (F/2115-1), Fundação Jose Bonifacio-UFRJ (Br.) (grant no. 4825-9). Fellowship from CNPq-Br (E.J.B. [30.1519/78 and 38.0710/91-3] and L.R.S.D.) is greatfully acknowledged. We thank Prof. Anibal L. Pereira for his valuable contribution to the QSAR study. We also thank the analytical centers of UFRRJ-Br and NPPN-Br, and Prof. R.S. Gil (UFRJ) for NMR spectra.

References

Bare, T.M., McLaren, C.D., Campbele, J.B., Firor, J.W., Resch, J.F., Walters, C.P., Salama, A.J., Miners, B.A. and Patel, J.B. (1989) Synthesis and structure activity relationships of a series of pyrazolo pyridine ester and amide anxiolytic agents. J. Med. Chem. 32, 2561–2573.

Barreiro, E.J. (1991) Bioisosterismo: Importante estratégia de modificação molecular para o planejamento racional de medicamentos. Rev. Bras. Farm. 72, 2–7 and 34–38.

Coburn, R.A. (1987) Dept. Med. Chem., School of Pharmacy, University of Buffalo, Buffalo, NY, 14260, USA.

de Lima, M.E.F. and Barreiro, E.J. (1992) The synthesis and anti-inflammatory properties of a new sulindac analogue synthesized from natural safrole. J. Pharm. Sci. 58, 1219–1222.

Dias, L.R.S., Pereira, A.L. and Barreiro, E.J. (1993) Relações entre a estrutura e atividade analgésica de derivados 5-acil-aril hidrazono pirazolo [3,4-b] piridina. Abstracts of 16ª Reunião Anual da Sociedade Brasileira de Química, Braz. Chem. Soc., Caxambu, Brazil, Abstr. SA-12.

Dias, L.R.S. (1992) Abstracted from the M.Sc. Thesis, Universidade Federal do Rio de Janeiro, Rio de Janeiro, Brazil.

Ferreira, S.H., Moncada, S. and Vane, J.R. (1973) Prostaglandins and the mechanism of analgesia produced by aspirin-like drugs. Br. J. Pharmacol. 49, 86–87.

Forbes, I.T., Johnson, C.N., Jones, G.E., London, J., Nicholas, J.M., Thompson, M. and Upton, N. (1990) Synthesis and evaluation of a series of aryl fused pyrazolo [4,3-c] pyridines with anxiolytic activity. J. Med. Chem. 33, 2540–2645.

Fraga, C.A.M. and Barreiro, E.J. (1992) The synthesis of a new benzothiazine derivative, related to oxicams, synthesized from natural safrole [1]. J. Heterocycl. Chem. 29, 1667–1669.

Freifelder, M. (1971) Practical Catalytic Hydrogenation Techniques and Applications. Wiley Interscience, New York, NY, pp. 451–456.

Freitas, A.C.C. and Barreiro, E.J. (1992) Synthesis of pyrazole derivatives as potential bioisosteres of thromboxane-synthese inhibitors. J. Heterocycl. Chem. 29, 407–411.

Higs, G.A., Eakings, K.E., Mugridge, K.G., Moncada, S. and Vane, J.R. (1980) The effects of non-steroid anti-inflammatory drugs on leucocyte migration in carragenin-induced inflammation. Eur. J. Pharmacol. 66, 81–86.

Kalsi, R., Pande, K., Bhala, T.N., Barthwal, J.P., Gupta, G.P. and Parmar, S.S. (1990) Antiinflammatory activity of quinazolino formazans. J. Pharm. Sci. 79, 317–320.

Khan, M.A. and Freitas, A.C.C. (1983) Hetarylpyrazoles IV. Syntheses and reactions of 1-5'-bipyrazoles. J. Heterocycl. Chem. 20, 277–279.

Lynch, B.M., Khan, M.A., Teo, H.C. and Pedrotti, F. (1988) Pyrazolo [3,4-b] pyridines: synthesis, reactions and nuclear magnetic resonance spectroscopy. Can. J. Chem. 66, 420–428.

Matheus, M.E., Oliveira, L.F., Freitas, A.C.C., Carvalho, A.M.A.S.P. and Barreiro, E.J. (1991) Antinociceptive property of new 4-acylarylhydrazone pyrazole compounds. Braz. J. Med. Biol. Res. 24, 1219–1222.

Miranda, A.L.P., Dias, L.R.S., Alvim, M.J.F. and Barreiro, E.J. (1993) Atividade antinociceptiva de derivados pirazolo [3,4-b] piridina. Abstracts of VIII Reunião Anual da Federação de Sociedades de Biologia Experimental, Caxambu, Brazil, Abstr. L.10.5.

Murray, W.V., Hadden, S.K. and Wachter, M.P. (1990) Synthesis of 3-(1,5-diphenyl-3-pyrazolyl)-aryl propanoates. J. Heterocycl. Chem. 27, 1933–1940.

Rodrigues, C.R., Alencastro, R.B., Freitas, A.C.C. and Barreiro, E.J. (1993) An AM1 study of 5-hydrazonopyrazole derivatives of biological interest. Abstracts of VII Simpósio Bras. Química Teorica, Braz. Soc. Chem., Caxambu, Brazil, Abstr. 31.

Silva, E.F. and Barreiro, E.J. (1993) The synthesis and antiinflammatory activity of 1-alkyl-isochroman-1-yl acetic acids derivatives. J. Braz. Chem. Soc. 4, 40–44.

Silveira, I.A.B.F., Paulo, L.G., Miranda, A.L.P., Rocha, S.O., Freitas, A.C.C. and Barreiro, E.J. (1991) Substituted pyrazolyl hydrazones: a new class of platelet aggregation inhibitors. Braz. J. Med. Biol. Res. 24, 947–951.

Silveira, I.A.B., Paulo, L.G., Miranda, A.L.P., Rocha, S.O., Freitas, A.C.C. and Barreiro, E.J. (1993) New pyrazolylhydrazone derivatives as inhibitors of platelet aggregation. J. Pharm. Pharmacol. 45, 646–649.

Sincholle, D., Bertez, C., Legrand, A., Conduzorques, J.P. and Bonne, C. (1987) Antiinflammatory activity of a dual inhibitor of cycloxygenase and lipoxygenase pathways, CBS-1108 (2-acetyl thiophene-2-thiazolythydrazone). Arzneim. Forsch. 35, 1260–1263.

Szileigyl, G., Kasztreiner, E., Matyus, P., Kosary, J., Czakc, K., Czeh, G., Huszti, Z., Tardos, L., Kcsa, E. and Jaszlits, L. (1984) Synthesis and antihypertensive activity of novel 6-substituted-3-pyridazinylhydrazone. Eur. J. Med. Chem. 19, 111–117.

Tihany, E., Feher, O., Gal, M., Janaky, J., Tolnay, P. and Sebestyen, L. (1984) Pyrazolecarboxylic acid hydrazides as antiinflammatory agents. New selective lipoxygenase inhibitors. Eur. J. Med. Chem. 19, 433–439.

Vane, J.R. (1971) Inhibition of prostaglandin synthesis as a mechanism of action for aspirin-like drugs. Nature New Biol. 231, 232–237.

Whittle, B.A. (1964) The use of changes in capillary permeability in mice to distinguish between narcotic and non-narcotic analgesics. Br. J. Pharmacol. 22, 246–253.