Pergamon

Bioorganic & Medicinal Chemistry Letters, Vol. 4, No. 2, pp. 377-380, 1994
Elsevier Science Ltd

0960-894X/94 $6.00+0.00

0960-894X(93)E0092-F

POSSIBLE ANTINEOPLASTIC AGENTS : PART 14 - SYNTHESIS, ACTIVITY AND QSAR STUDIES OF SOME 1-(SUBSTITUTED BENZENESULPHONYL)-5-OXOPYRROLIDINE-2-CARBOXYLIC ACID HYDRAZIDES

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Abstract : Eight 1-(substituted benzenesulphonyl)-5-oxopyrrolidine-2-carboxylic acid hydrazides have been synthesized in the QSAR operational scheme and tested for antineoplastic activity in Swiss albino mice with Ehrlich ascites carcinoma (EAC) cell line. The values of percent inhibition of growth, both in ascitic cell count and fluid weight, have been taken as activity parameters. Results indicate that phenylhydrazides are more active than the simple hydrazide analogs. Amongst the phenylhydrazides the unsubstituted compound is the most active one. QSAR has been studied using the LFER model.

The rationale behind our continued search for possible antineoplastic agents amongst the glutamic acid analogs such as glutarimides, glutaramides, glutamic acids, glutaramic acids, glutamines etc. has been earlier discussed.[1-5] 1-(Substituted benzenesulphonyl)-5-oxopyrrolidine-2-carboxylic acid **[4]** might be regarded either as the precursor or cyclized variant of glutamic acids. Furthermore, this has striking structural similarity with tenuazonic acid **[1]**, an antibiotic, which shows its antineoplastic activity by inhibiting the protein synthesis and preventing the release of newly formed proteins.[6,7]

Here we report the biological evaluation results of a few 1-(substituted benzenesulphonyl)-5-oxopyrrolidine-2-carboxylic acid hydrazides **[6]** and phenylhydrazides **[7]** prepared as shown in scheme 1. Structural variants in the aromatic ring are 4-chloro, 3,4-dichloro and 4-methyl. Altogether eight compounds have been prepared under this series. Details of preparations have been avoided becaused of their straightforward nature.

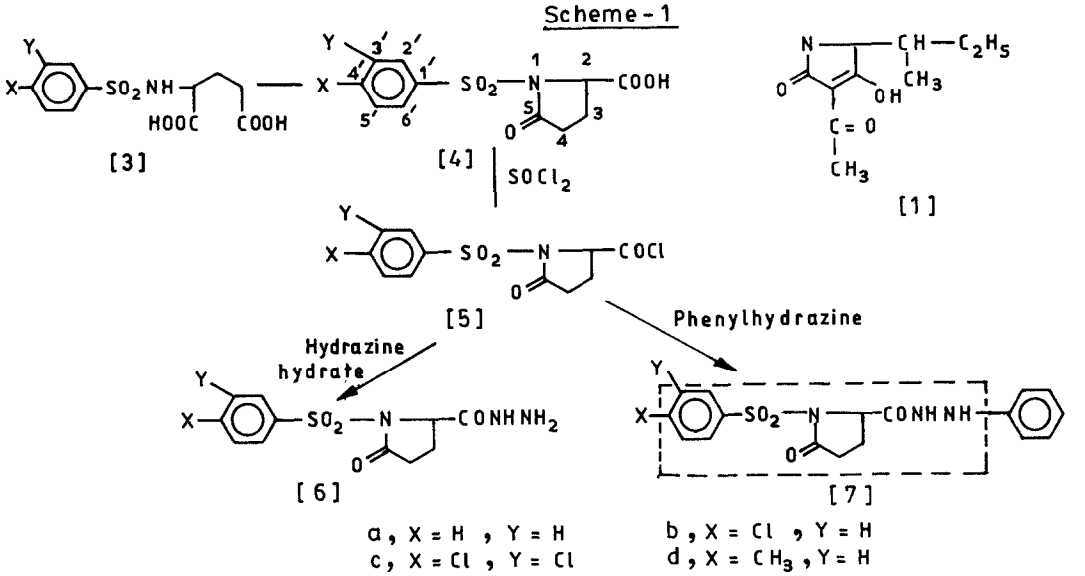
All the melting points are uncorrected. Structural characterization of these compounds has been based on elemental analysis, IR and ^{1}H NMR survey spectrum. Biological evaluation was by the procedure reported previously from this laboratory[1] and QSAR studies were performed using the Hansch method.

Synthesis - 4-Chlorobenzenesulphonyl chloride and 3,4-dichlorobenzenesulphonyl chloride **[2]** were prepared by chlorosulphonation of chlorobenzene and 1,2-dichlorobenzene respectively.[8] 2-(Substituted benzenesulphonyl)-L-glutamic acids **[3]** and 1-(substituted benzenesulphonyl)-5-oxopyrrolidine-2-carboxylic acids **[4]** were prepared as reported earlier.[3-5]

1-(Substituted Benzenesulphonyl)-5-Oxopyrrolidine-2-Carboxylic Acid Hydrazides [6a-6d] - A mixture of 1-(substituted benzenesulphonyl)-5-oxopyrrolidine-2-carboxylic acid (0.05 mole)

and thionyl chloride (10 ml) was refluxed on a steam bath for 2 h and excess thionyl chloride was removed to furnish the corresponding acid halides **[5]**. To it dry benzene (10 ml) was added and the reaction vessel was cooled to 10^{o} in an ice bath when hydrazine hydrate (80% w/w; 0.05 mole) was added dropwise with vigorous stirring. After the reaction was over the solid mass was first washed with sodium bicarbonate solution (5% w/v) to remove any unreacted acid and finally washed with water. The residual mass was crystallized from ethanol (90%) with charcoal treatment. Physical characteristics are recorded in Table 1.

Scheme-1



1-(Substituted Benzenesulphonyl)-5-Oxopyrrolidine-2-Carboxylic Acid Phenylhydrazides [7a-7d]- To the acid halides **[5]** prepared from 1-(substituted benzenesulphonyl)-5-oxopyrrolidine-2-carboxylic acid (0.05 mole) and thionyl chloride (10 ml), dry benzene (10 ml) was added and the reaction vessel was cooled to 10^{o} in an ice bath when phenylhydrazine (97.5% w/w; 0.05 mole) was added dropwise with vigorous stirring. After the reaction was over the solid mass was first washed with sodium bicarbonate solution (5% w/v) to remove any unreacted acid and finally with water. The residual mass was crystallized from petroleum ether (60^{o}-80^{o}) with charcoal treatment Physical characteristics are recorded in Table 1.

Pharmacology - The *in vivo* antineoplastic activities of the synthesized compounds were evaluated against Ehrlich ascites carcinoma (EAC) cell in Swiss albino mice of body weight (18-20 g). Both inhibition in cell count and tumor weight were determined following the procedures reported earlier.[1] The compounds were administered i.p. at a dose of 50 mg/kg body weight at pH 7.4. Mitomycin-C at a dose of 1 mg/kg i.p. was used as a standard. The dose was selected on the basis of the experimentally determined LD_{50} values of the compounds. The results of biological evaluation are recorded in Table 1.

Results and Discussion : Having considered the limitation of data points from QSAR angle, eight in this case, only an exploratory QSAR analysis by way of Hansch approach was performed on the eight synthesized compounds just to have a glimpse, only a tentative one, of any existing correlation. And in this process the biological activity, percent inhibition of ascitic fluid weight, was converted to their logit values[9]:

$$B_A = \frac{MW}{d} \log \frac{P}{100-P} \quad \ldots\ldots\ldots \quad (1)$$

where B_A is the biological activity in mM^{-1}, MW the molecular weight of the compound, d the daily i.p. dose in mg/kg body weight of the mice, and P the percent inhibition of ascitic fluid weight. Hansch's π, the hydrophobic parameter, Hemmett's σ, the electronic parameter and molar refractivity, MR, the steric parameter were used as predictor variables (Table 1), e.g.,

$$\pi = \pi_{Ar} + \pi_{Ali}$$
$$\sigma = \sigma_x + \sigma_y$$
$$MR = MR_{Ar} + MR_{Ali}$$

where π represents the combined hydrophobic contribution of the aromatic and aliphatic parts, σ represents the electronic contribution of the aromatic substituents X and Y, and MR represents the combined steric contribution of the aromatic and aliphatic parts. Regression analysis was carried out on a CYBER 180/840 A mainframe computer under NOS/VE environment using IMSL/STAT Library subroutines.[10] The inter correlation matrix (r) of the predictor variables as well as B_A is:

	σ	MR	B_A
π	0.423	0.965	0.440
σ		0.214	-0.108
MR			0.578

Bivariate regression as well as dissection into aliphatic and aromatic parts did not yield any meaningful correlation, quite expectedly due to lesser degrees of freedom. Hence, univariate regression was attempted with all the parameters individually and equation (2) was obtained out of several:

$$B_A = \underset{0.8758}{0.179\ (1.100)} + \underset{0.1400}{7.853\ (4.619)}\ MR \quad \ldots\ldots\ldots \quad (2)$$

n = 8, r = 0.578, EV = 21.266, SEE = 1.655, F (1,6) = 2.891 (86% confidence level).

Where, n is the number of data points, r the linear correlation coefficient. EV the explained variance, SEE the standard error of estimates and F the variance ratio with 1 and 6 degrees of freedom. A regression constant is followed by its standard error in parenthesis while the probability of larger/t/is given below it.

Evidently, it is a poor correlation but offers the scope for a better one. On inspection it has been found that the compound 7a and 7c are outliers and if these are

dropped from the regression exercise then the equation (3) results which bears a meaning:

$$B_A = \underset{0.7836}{-0.132\ (0.449)} + \underset{0.0200}{8.453\ (2.254)}\ MR \quad \ldots\ldots\ldots (3)$$

n = 6, r = 0.882, EV = 72.313, SEE = 0.6507, F (1,4) = 14.059 (98% confidence level).

It is apparent from equation (3) that the steric factor, MR, both aromatic and aliphatic, plays a significant role in this class of compounds and this observation is in conformity with our earlier findings.[12]

Table 1. Physical properties, substituent's physicochemical parameters and antineoplastic activity of synthesized compounds.

Compound No.	m.p. (°C)	Yield (%)	Physicochemical parameters[1] π	σ	MR[2]	% Inhibition of ascitic Cell	Fluid	B_A Observed[3]	Calculated[4]
6a	263-265	64.2	0.23	0.00	0.0309	40.33	44.44	-0.549	0.129
6b	268-270	48.6	0.94	0.23	0.0809	64.92	61.11	1.246	0.552
6c	258-260	43.9	1.65	0.60	0.1309	59.34	58.33	1.028	0.974
6d	247-249	57.6	0.79	-0.17	0.0771	50.08	52.78	0.610	0.520[5]
7a	213-215	60.4	1.90	0.00	0.2742	78.99	85.71	5.586	2.186
7b	207-209	35.6	2.61	0.23	0.3242	74.29	71.43	3.132	2.608[5]
7c	218-220	26.4	3.32	0.60	0.3742	66.85	57.71	1.155	3.031
7d	235-237	15.0	2.46	-0.17	0.3204	77.57	64.28	1.893	2.576
Mitomycin-C (Standard)						100.00	100.00		

(1) Values taken from reference 11 (Table VI-1 & VI-2, Chapter VI); (2) Equiscaled by the factor 0.01; (3) Observed biological activity converted into logit model (mM^{-1}) by equation 1; (4) Biological activity calculated from equation 3; (5) Outliers.

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(Received in USA 29 April 1993; accepted 22 October 1993)