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Pharmacological effects of some 6-azauracil derivatives

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6-AZAURACIL (I) (2,3,4,5-tetrahydro-1,2,4-triazine-3,5-dione) was examined for its antitumoral properties by Sorm and Skoda[1] and by Handschumacher and Welch[2] in 1956. A series of 6-azauracil derivatives[4, 5] were synthesized at the Institute of Pharmaceutical Research in Bucharest and their pharmacological properties are reported in the present paper.

MATERIAL AND METHOD

The tests using mice, rats and dogs were performed according to a methodology that was presented in detail in a previous paper.[6] Acute toxicity by determination of LD_{50} by the probit method or that of the maximum tolerated dose (MTD) by intraperitoneal or subcutaneous administration. Neurotropic activity produced by a single dose (1/10 of LD_{50} or 1/5 of MTD in mice), using:

(1) the traction test,[7] the chimney test[8] or the perforated plate test[9] for the determination of locomotor sedation;
(2) the anticonvulsive activity against pentamethylenetetrazol (125 mg/kg body weight i.p.) or electroshock (42 V, 0·3 sec);
(3) interaction with barbiturate sleep (amytal, 75 mg/kg body weight);
(4) pain stimulus (the test of the heated plate);[10] and
(5) thermic reactivity (variations in the body temperature measured by a thermocouple with an oral electrode).

Activity on the cardiovascular and vegetative nervous system. Determination of blood pressure reactivity in chloralized dogs followed the intravenous administration of a single dose (1/10 of LD_{50}) or repeated doses of the investigated substances. Modifications in blood pressure and cardiac rhythm, reactivity to chemical mediators (adrenaline, noradrenaline, serotonin, acetylcholine, histamine), sympathetic ganglio reactivity, the carotid pressor reflex were also studied.

Activity on the urinary system. Determined by the fluid excretion and in certain cases of electrolyte elimination, during 5 hr, in hydrated animals.

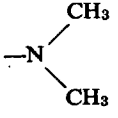
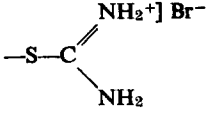
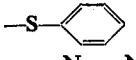
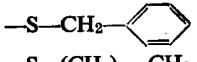
Comparative investigations were carried out on groups of normal control animals, kept under the same experimental conditions and tested concomitantly. The pharmacological results were expressed quantitatively by a conventional notation in accordance with the intensity of the investigated activity.

RESULTS

The results presented in Table 1 show that only the derivatives II, IV, X, XI had a toxicity near to or less than that of azauracil (I). Derivatives V and VIII proved to be the most toxic. Azauracil had a slight sedative effect but some of the derivatives (VII, X, XI, XII) had a more marked neurodepressant activity at several levels (XI and XII) which displayed anticonvulsive properties. None of the substances using doses of (1/10 of LD_{50}) caused but more than insignificant modifications of the arterial pressure. With respect to the reactivity to chemical mediators, derivatives X and XI had a slight cholinergic and antihistamic effect of very short duration. The carotid sinus pressor reflex was not abolished at any time following the administration of the triazine derivatives investigated. The investigation of the diuretic activity of the triazine derivatives revealed a diuretic effect of derivative VII and an antiduiretic effect of derivative VI.

Welch's investigation[11] on the pharmacology of azauracil revealed the neurotropic activity of its derivatives that induce hypnosis, muscular relaxation and analgesia in animals when a dose of 1–3 g/kg is administered. Welch's investigations as well as Chang's investigations[12] with alkyl-replaced azauracil derivatives show that the effect on the CNS is due to the triazine ring itself and that the longer the lateral chain (up to 7 carbons), the higher the hypnotic effect with the simultaneous increase of the solubility in non-polar solvents, which allows easier penetration of the blood brain

TABLE 1. ACUTE TOXICITY AND NEUROTROPIC ACTIVITY OF 6-AZAURACIL DERIVATIVES

No.	R =		LD_{50} (mg/kg)		Dose given (mg/kg)	Sedative effect	Anticonvulsive effect		Sleep potentiation	Decrease in pain excitability (analgesia)	Hypothermia
							Electroshock	Cardiazol			
I	—H	6-Azauracil	1612 2076	i.p. s.c.	200	+	0	0	+	0	0
II	—Br	5-Brom-6-azauracil	1771 2568	i.p. s.c.	180	+	0	0	+	0	0
III		5-morpholil-6-azauracil	776	i.p.	80	0	0	0	0	0	0
IV		5-dimethyl-amino-6-azauracil	880	i.p.	90	0	0	0	0	0	0
V		6-azauracil-5-iso-thiouronium-bromhydrat	267	s.c.	27	0	0	0	0	0	0
VI	—S—Na	5-mercapto-6-azauracil	2917	i.v.	1000	0	0	0	0	0	0
VII		5-phenyl-thio-6-azauracil	692 832	i.p. s.c.	70	++	0	+	0	0	+
VIII		5(2′-amino-1′,3′,4′,-thiodiazol-5′)-thio-6-azauracil	21	s.c.	25	+	0	0	+	0	0
IX	—S—CH_2—CH=CH_2	5-allyl-thio-6-azauracil	884	s.c.	90	0	0	0	0	0	0
X		5-benzyl-thio-6-azauracil	1420	i.p.	140	++	+	0	0	0	++
XI	—S—$(CH_2)_5$—CH_3	5-hexyl-thio-6-azauracil	1660	i.p.	170	++	++	+	+	0	+
XII	—S—$(CH_2)_3$—CH_3	6-butyl-thio-6-azauracil	781	i.p.	80	++	+	+	0	0	++

barrier. Our investigations confirmed that the neurodepressant activity depends on the length of the chain (number of C atoms in position 6). The presence of an aromatic ring in the terminal position of the lateral chain at C6 does not prevent the neurodepressant effect (VII, X) but the presence of other rings eliminates it (III, IV, VIII). It is interesting to note that all neurodepressants were mercapto-derivatives of azauracil and that the intercalated presence of sulphur did not influence the intensity of the neurotropic effect when the lateral chain was long enough. In the case of short chains or in the absence of any lateral chain (VI) the neurotropic activity was abolished.

Derivative XI is a derivative with a 6 C chain that confers on it a marked affinity for the nervous system. Its neurodepressant effects determined the thorough study of certain pharmacodynamic aspects using a large range of doses in order to study its anticonvulsive activity. It should be noted that the product was able to reduce the convulsive threshold, to increase the latency in the appearance of cardiazol convulsions and to prevent the tonic phase of convulsions, following both parenteral and oral administration. However, by combining XI with phenobarbital at sub-threshold doses, only a summation of their activities was obtained until potentiation phenomena appeared.

As regards the diuretic effect of VII it should be stressed that the diuretic activity of diazine derivatives (Aminometradine, Aminoizometradine) and of sym-triazine derivatives (Orpidan, Amanozine)[13, 14] was reported, but that there was no mention of a diuretic activity in asym-triazine derivatives. Detailed investigations carried out with VII which will be reported subsequently revealed important diuretic and saluretic activity and a dose of 75 mg/kg given orally increased the elimination of sodium ions by 176 per cent, of potassium ions by 78 per cent, and of chloride ions by 79 per cent.

In summary, the screening tests carried out with a series of 6-azauracil derivatives revealed a series of substances with a neurotropic or diuretic activity.

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