DOI 10.1007/s11094-017-1534-2
Pharmaceutical Chemistry Journal, Vol. 50, No. 12, March, 2017 (Russian Original Vol. 50, No. 12, December, 2016)

ANTIPROLIFERATIVE ACTIVITY OF CYANO-SUBSTITUTED PYRANS AND 1,2,5,6,7,8-HEXAHYDROQUINOLINE-3,3,4,4-TETRACARBONITRILES

M. A. Mar'yasov,[1] V. P. Sheverdov,[1] V. V. Davydova,[1] and O. E. Nasakin[1]

Translated from Khimiko-Farmatsevticheskii Zhurnal, Vol. 50, No. 12, pp. 26 – 27, December, 2016.

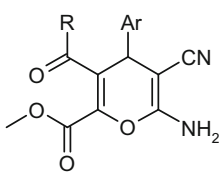
Original article submitted July 19, 2016.

The antiproliferative activity of methyl-6-amino-3-acyl-4-aryl-5-cyano-4*H*-pyran-2-carboxylates, 9-aryl-12-imino-10,11-dioxatricyclo[5.3.2.0^{1,6}]dodecane-7,8,8-tricarbonitriles, and 1,2,5,6,7,8-hexahydroquinoline-3,3,4,4-tetracarbonitriles was investigated.

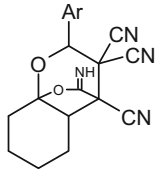
Keywords: methyl-6-amino-3-acyl-4-aryl-5-cyano-4*H*-pyran-2-carboxylates, 9-aryl-12-imino-10,11-dioxatricyclo[5.3.2.0^{1,6}]dodecane-7,8,8-tricarbonitriles, and 1,2,5,6,7,8-hexahydroquinoline-3,3,4,4-tetracarbonitriles, tetracyanoethylene, arylidenemalononitriles, antiproliferative activity.

Polycyano-substituted carbo- and heterocycles that we synthesized earlier possessed antitumor properties [1]. High antitumor activity for compounds with hydroxyl, methoxyl, methoxycarbonyl, and cyano groups would be predicted from the literature [2 – 6].

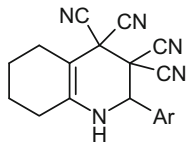
Methyl-6-amino-3-acyl-4-aryl-5-cyano-4*H*-pyran-2-carb oxylates (**I**) were prepared by reacting 2-arylidenemalononitriles with methyl-2,4-dioxobutanoates [7]. 9-Aryl-12-imino-10,11-dioxatricyclo[5.3.2.0^{1,6}]dodecane-7,8,8-tricarb onitriles (**II**) were synthesized from cyclohexanone tetracyanoethylene adduct and aldehydes by the usual method [8]. Reactions of cyclohexanone tetracyanoethylene adducts with 1,3,5-tri-substituted 2,4-diazapenta-1,4-dienes by the literature method [9] gave 1,2,5,6,7,8-hexahydroquinoline-3,3,4,4-tetracarbonitriles (**III**).



I



II



III

I: Ar = 3,4,5-$(MeO)_3C_6H_2$ (a, b, c), 4-$MeOOCC_6H_4$ (d), 2-F-6-ClC_6H_3 (e); R = Me (a), 2-Fu (b), 3,4-$(MeO)_2C_6H_3$ (c), 4-BrC_6H_4 (d), 3,4-$(MeO)_2C_6H_3$ (e).
II: Ar = 3,4,5-$(MeO)_3C_6H_2$ (a), 3-MeO-4-HOC_6H_3 (b), 4-$MeOOCC_6H_4$ (c), 4-$(CH_3)_2NC_6H_4$ (d).
III: Ar = 4-$MeOC_6H_4$ (a), 2-Thienyl (b).

[1] I. N. Ul'yanov Chuvash State University, Cheboksary, Chuvash Republic, 428010, Russia; e-mail: sheverdovvp@yandex.ru

Antiproliferative activity of cyano-substituted **I-III** was studied at the National Cancer Institute (USA) using an *in vitro* model that allowed the experimental conditions to be standardized for repetitive series according to the NCI-60 One-Dose Screen protocol [10]. The studies used 60 tumor cell lines [11] from human lung, colon, brain, ovary, kidney, prostate, breast, leukemia, and melanoma. Results were processed statistically using the Student *t*-criterion. An effect was considered statistically significant for $p < 0.05$. It was found that **IIIa** [2-(4-methoxyphenyl)-1,2,5,6,7,8-hexahydroquinoline-3,3,4,4-tetracarbonitrile] had the most promising antiproliferative activity for further research (Table 1). **IIIa** at a concentration of 10^{-5} M showed significant inhibition of tumor cell growth.

The test results showed that substituted tetracarbonitrile **IIIa** was most active against leukemia cell lines because it suppressed considerably growth of all test cultures [CCRF-CEM, HL-60(TB), K-562, MOLT-4, RPMI-8226, SR]. The average inhibition of these cell lines was 74.91%; maximum, 98.88% (SR).

Thus, substituted tetracarbonitrile **IIIa** at a concentration of 10^{-5} M was much more active than known antitumor preparations such as busulfan and cisplatin.

The high alkylating capability of cyano groups with respect to various nucleophiles [12, 13] suggested that the

TABLE 1. Antiproliferative Activity of Compounds (10^{-5} M) (from One-Dose Screen Program)

Compound	% Inhibition of cell lines								
	leukemia	lung cancer	colon cancer	brain cancer	melanoma	ovary cancer	kidney cancer	prostate cancer	breast cancer
Ia	–	14.19 ± 1.12	–	14.98 ± 1.29	11.36 ± 1.02	–	–	–	–
Ib	–	–	–	19.33 ± 2.01	–	–	12.15 ± 1.36	–	–
Ic	–	14.51 ± 1.31	–	–	–	–	11.23 ± 1.07	–	–
Id	–	16.34 ± 1.75	–	–	12.06 ± 1.17	–	15.11 ± 1.34	–	–
Ie	–	14.28 ± 1.57	–	11.00 ± 1.05	–	–	14.44 ± 1.49	–	–
IIa	37.09 ± 3.21	13.24 ± 1.17	–	18.65 ± 1.36	15.50 ± 1.28	–	14.84 ± 1.16	–	16.87 ± 2.17
IIb	25.02 ± 2.85	12.80 ± 1.09	–	11.37 ± 1.04	–	–	18.27 ± 2.09	–	18.21 ± 2.07
IIc	13.45 ± 1.42	13.91 ± 1.48	–	–	12.44 ± 1.24	–	–	–	15.41 ± 1.59
IId	13.12 ± 1.39	11.89 ± 1.14	–	–	17.73 ± 1.91	–	–	–	10.93 ± 1.01
IIIa	74.91 ± 3.80	43.98 ± 3.05	53.86 ± 3.51	11.48 ± 1.08	26.47 ± 1.12	57.04 ± 3.05	29.10 ± 2.24	–	43.22 ± 2.35
IIIb	53.75 ± 3.48	29.17 ± 2.54	31.07 ± 2.68	–	13.31 ± 1.45	40.54 ± 2.69	31.57 ± 2.52	–	23.51 ± 2.06
Busulfan, solution for i.v. injection, Otsuka Pharm	–	–	–	–	18.80 ± 1.98	–	–	–	–
Cisplatin, powder for solution preparation, Corden Pharma Latina S.p. A.	–	32.1 ± 2.15	–	13.90 ± 1.31	14.2 ± 1.10	26.90 ± 1.87	18.10 ± 1.72	19.90 ± 2.05	10.90 ± 1.03

antiproliferative activity of the compounds could be due to cyanoalkylation of nucleophilic sites on tumor-cell DNA molecules. Furthermore, the steric positioning of the cyano groups in the ethyl-1,1,2,2-tetracarbonitrile moiety is favorable for rapid coordination to nucleophilic sites, which accelerates the cyanoalkylation.

The results confirmed our hypothesis that the ethyl-1,1,2,2-tetracarbonitrile moiety in the cyclic compounds was a pharmacophore.

ACKNOWLEDGMENTS

The work was sponsored by RSF Grant No. 15-13-10029.

REFERENCES

1. V. P. Sheverdov, A. Yu. Andreev, O. E. Nasakin, and V. L. Gein, *Khim.-farm. Zh.*, **48**(6), 25 – 28 (2014); *Pharm. Chem. J.*, **48**(6), 379 – 382 (2014).
2. G. G. Dubinina, M. O. Platonov, S. N. Golovach, et al., *Eur. J. Org. Chem.*, **41**(6), 727 – 737 (2006).
3. B. Song, *J. Fluorine Chem.*, **126**, 87 – 92 (2005).
4. S. A. F. Rostom, G. S. Hassan, and H. I. El-Subbagh, *Arch. Pharm. Chem. Life Sci.*, **342**, 584 – 590 (2009).
5. U. W. Hawas, *Am. J. Appl. Sci.*, **8**(10), 945 – 952 (2011).
6. J.-N. Chen, X.-F. Wang, T. Li, et al., *Eur. J. Med. Chem.*, **107**, 12 – 25 (2016).
7. V. P. Sheverdov, A. Yu. Andreev, O. V. Ershov, et al., *Khim. Geterotsikl. Soedin.*, No. 7, 1073 – 1082 (2012).
8. Ya. S. Kayukov, P. M. Lukin, O. E. Nasakin, et al., *Khim. Geterotsikl. Soedin.*, No. 4, 497 – 499 (1997).
9. Ya. S. Kayukov, O. E. Nasakin, Ya. G. Urman, et al., *Khim. Geterotsikl. Soedin.*, No. 10, 1395 – 1410 (1996).
10. A. Monks, D. Scudiero, et al., *J. Natl. Cancer Inst.*, **83**(11), 757 – 766 (1991).
11. https: // dtp.cancer.gov / discovery_development / nci-60 / cell_list.htm
12. Ya. S. Kayukov, *Russ. J. Org. Chem.*, **47**(3), 392 – 401 (2011).
13. Ya. S. Kayukov, *Russ. J. Org. Chem.*, **48**(4), 491 – 493 (2012).