Pergamon

Bioorganic & Medicinal Chemistry Letters, Vol. 7, No. 24, pp. 3149-3152, 1997

0960-894X/97 $17.00 + 0.00

PII: S0960-894X(97)10155-X

POLYSUBSTITUTED 2H-PYRAN-2-ONES : A NEW CLASS OF HEPATOPROTECTIVE AGENTS+

Vishnu J. Ram*, Navedul Haque, Mahendra Nath, Sunil K. Singh, Falak A. Hussaini, S.C. Tripathi, A. Shoeb

Central Drug Research Institute, Lucknow 226 001, India

Abstract : The synthesis and hepatoprotective activity of 6-aryl-3-substituted-4-methylthio-2H-pyran-2-ones (**3, 5, 7**) and the corresponding 2-thiones (**6**), 6-aryl-4-methylthio-2H-pyran-2-ones (**4**) and 6-aryl-3-carbethoxy-5-cyano-4-methylthio-2H-pyran-2-ones are described. © 1997 Elsevier Science Ltd.

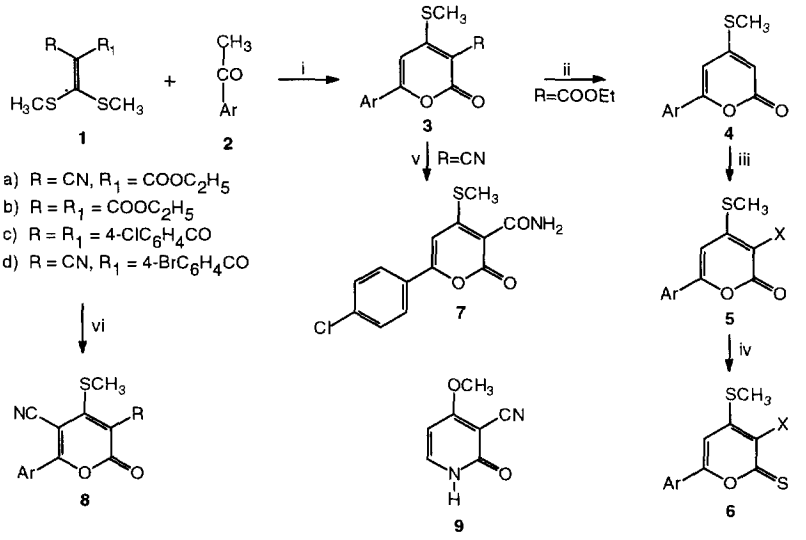
Perpetual exposure of liver to xenobiotics and therapeutic agents leading to toxic manifestations of complex and diverse nature, on one hand and paucity of any safe medication on the other, renders the management of hepatic disorders more problematic. The use of some synthetic and semisynthetic drugs which include steroids, immunosuppressive agents and antiviral drugs such as corticosteroids, acyclovir, vidrabin alone or in combination with a-interferon, has been a subject of controversy and met with limited survival rates. Besides the risk of relapse and side effects, these provide only symptomatic relief and have little influence on the disease process itself.

Many herbal formulations, whose efficacies are long known, yet little understood, are claimed to be effective in hepatic diseases. Several class of natural products[1], comprising the constituents of herbs in the formulation, various sulfur compounds[2-4] display pronounced hepatoprotective activity and many of these possess pyran-2- or 4-one moieties either in a rigid or flexible form. Recently, 3-cyano-4-methoxy-1H-pyridin-2-one[1b] (**9**), isolated from *Ricinus cummunis*, was found to be effective at 6 mg/kg/p.o. dose with LD_{50} 80 mg/kg/p.o. in rats in various models of liver injuries. This provided a template for designing and eventual emergence of the present new class of hepatoprotectants[5,6]. Accordingly, retaining some of the structural features of **9** on 2H-pyran-2-one or the corresponding thione ring skeletons, permitted in identifying a series of 6-aryl-3-carbethoxy-, 6-aryl-3-cyano-, and 6-aryl-3-carboxamido-4-methylthio-2H-pyran-2-ones (**3, 7**), 6-aryl-3-halo-4-methylthio-2H-pyran-2-ones (**5**) and the corresponding thiones (**6**), 6-aryl-4-methylthio-2H-pyran-2-ones (**4**) and 6-aryl-3-carbethoxy-5-cyano-4-methylthio-2H-pyran-2-ones (**8**) [Scheme 1] to be effective in liver injuries. Among these, the 6-(4-chlorophenyl)-3-cyano-4-methylthio- and 3-bromo-6-(4-chlorophenyl)-4-methylthio-2H-pyran-2-ones (**3b, 5d**) were most potent of the series.

All the synthesized compounds listed in Table 1 were screened for their hepatoprotective activity against thioacetamide-induced hepatic damage in rats. The activity of the compounds was assessed on the basis of % protection afforded in various levels of serum enzymes such as glutamate pyruvate transaminase

+CDRI Communication No. 5248

Scheme 1



Reagents and conditions: i) DMF/KOH or K_2CO_3/DMSO, RT; ii) PPA, 120°C; iii) NCS or NBS in CH_2Cl_2; iv) P_2S_5/Toluene; v) H_2SO_4, 60°C; vi) $NCCH_2COOC_2H_5$/DMSO/K_2CO_3

(GPT)[7], glutamate oxaloacetate transaminase[7](GOT), acid phosphatase[8](ACP), alkaline phosphatase[9](ALP) and glutamate dehydrogenase[10](GlDH). The results are presented in Table 1. The compound **3b** was studied in detail in different toxin-induced models and % protection is reported in Table 2. A study of structural requirements for activity in compounds **3 - 8**, revealed that substituents at C-3 and C-6 positions in the pyran ring play a pivotal role in expressing significant hepatic protection as adjudged by bringing stepwise change in the ring substituents.

A change in the 6-aryl substituents in **3 - 8** rendered the order of activity as 4-chlorophenyl > 2,4-dichlorophenyl > 4-bromophenyl > 4-fluorophenyl. Switching over from aromatics to heteroaromatics, the activity of moderate order was retained only in **3e, f**, while compounds with pyridyl substituents (**3g, h**) were devoid of activity.

Among the various substituents at C-3, the CN (**3a,h**), Br (**5c-g, 6b**) and Cl (**5a, b, 6b**) were found to optimise the activity in compounds bearing haloaryl, 2-thienyl or 2-furyl substituents at C-6 position. Shifting the CN group from C-3 to C-5 gave inactive compound (**8**). Compounds **3b** and **5d** were almost equipotent in offering protection in all the enzyme parameters due to closeness in the atomic volumes of CN (23.5) and Br (22.3). However, **5d** had an edge over **3b** in displaying better protection (GPT, ALP). Compounds without substituents at C-3 (**4a, b**) exhibited moderate hepatoprotective activity. Replacement of CN by $COOC_2H_5$ (**3i**) and $CONH_2$ (**7**) groups led to the loss of activity. Thus, it may be concluded that 6-haloaryl with 3-cyano or 3-bromo substituents at 4-methylthio-2H-pyran-2-one nucleus seem to be essential requirements for expressing hepatoprotective activity.

Table 1 : Hepatoprotective activity of **3 - 8** against thioacetamide induced toxicity in rats at 6 mg/kg (p.o. x 7 days). Values are the % protection afforded by the compounds

Compd.	Ar	R/X	GOT	GPT	ACP	ALP	GlDH
3a	4-FC_6H_4	CN	20	31	46*	15	0
3b	4-ClC_6H_4	CN	68**	69**	59*	65*	51*
3c	4-BrC_6H_4	CN	20	10	38	56*	40
3d	2,4-$Cl_2C_6H_3$	CN	37	45	61*	33	65**
3e	2-Thienyl	CN	37	74**	10	33	100**
3f	2-Furyl	CN	71**	72**	0	19	15
3g	3-Pyridyl	CN	12	12	38	0	51*
3h	4-Pyridyl	CN	0	0	0	12	0
3i	4-ClC_6H_4	$COOC_2H_5$	23	31	0	11	17
4a	4-FC_6H_4	H	59*	57*	46*	30	15
4b	4-ClC_6H_4	H	46*	51	24	42	43
5a	4-ClC_6H_4	Cl	36	51	38	40	27
5b	4-BrC_6H_4	Cl	30	40	30	19	26
5c	4-FC_6H_4	Br	0	0	49	43	0
5d	4-ClC_6H_4	Br	70**	80*	48*	100**	51*
5e	4-BrC_6H_4	Br	47*	18	72*	15	28
5f	2-Thienyl	Br	50*	55*	25	37	4
5g	4-Pyridyl	Br	48*	0	53*	12	16
6a	4-ClC_6H_4	Cl	29	26	25	10	12
6b	4-ClC_6H_4	Br	25	0	0	36	20
7	4-ClC_6H_4	$CONH_2$	16	15	10	17	0
8a	4-ClC_6H_4	$COOC_2H_5$	14	19	30	0	16
8b	4-BrC_6H_4	$COOC_2H_5$	0	0	2	0	2
	Silymarin (Standard drug)		50.14*	47.25*	43.25*	47*	38.81

**$P < 0.01$; *$P < 0.05$) as compared to toxin treated group.

Table 2 : Hepatoprotective activity of 6-(4-chlorophenyl)-3-cyano-4-methylthio-2H-pyran-2-one (**3b**) in different models at 6 mg/kg (p.o. x 7 days) is expressed in terms of % protection. Values in parentheses are due to Silymarin, used as a standard drug in identical conditions.

Models	GOT	GPT	ACP	ALP	GlDH
Galactosamine	86**	76**	66**	68*	57*
	(47)	(45)	(61)	(33)	(65)
Paracetamol	73**	81**	90**	73*	54*
	(46)*	(49)*	(67)*	(50)*	(60)*
Carbon Tetrachloride	59*	67*	70*	57*	58*
	(48)*	(64)*	(57)*	(51)*	(51)*
Alcohol	34	48	53*	24	40
	(43)	(59)*	(49)*	(62)*	(49)
Alcohol	58*	69**	74**	56*	62*
12 mg/kg (p.o. x 7 days)	(62)*	(78)*	(64)**	(77)**	(59)*

**P < 0.01; *P < 0.05 > as compared to toxin treated group.

Acknowledgement : NH, SKS and MN are thankful to CSIR, New Delhi for financial assistance.

References and Notes :

1. a) Handa, S.S.; Sharma, A.; Chakraborti, K.K.; *Fitoterapia*, **1986**, *57*, 307. b) Visen, P.K.S.; Shukla, B.; Patnaik, G.K.; Tripathi, S.C.; Kulshreshtha, D.K.; Srimal R.C.; Dhawan, B.N.; *Int. J. Pharmacognosy* (U.S.A.) **1993**, *30*, 241.
2. Allais, A.; Gisault, P.; *Chem. Abstr.*, **1969**, *71*, 91459.
3. Nakayama, S.; Okazaki, M.; Sakai, S.; Nakamura, Y.; Sakamoto, K.; *Showa Igakkai Zasshi*, **1979**, *39*, 19.
4. Saiga, Y.; Iijima, I.; Ishida, A.; Miyagishima, T.; Oh-ishi, T.; Matsumoto, M.; Matsuoka, Y.; *Chem. Pharm. Bull.*, **1987**, *35*, .2840 and 3262.
5. a) Tominaga, Y.; Ushirogouchi, A.; Matsuda, Y.; Kobayashi, G.; *Chem. Pharm. Bull.*, **1984**, *32*, 3384. b) Tominaga, Y.; Kawabe, M.; Hosomi, A.; *J. Heterocycl. Chem.*, **1987**, *24*, 1325. c) Tominaga, Y.; Ushirogouchi, A.; Matsuda, Y.; *J. Heterocycl. Chem.*, **1987**, *24*, 1557. d) Ram, V.J.; Verma, M.; Hussaini, F.A.; Shoeb, A.; *J. Chem. Res. (S)*, **1991**, 99.
6. Tominaga, Y.; *Trends in Heterocyclic Chemistry*, **1991**, *2*, 43.
7. Reitman, S.; Frankel, S.; *Am. J. Clin. Pathol.*, **1957**, *28*, 56.
8. Kind, P.R.N.; King, E.J.; *J. Clin. Pathol.*, **1954**, *7*, 322.
9. King, J.; Methods in Enzymatic Analysis; Bergmeyer, H.U.; Academic Press, New York, pp. 656, 1963.
10. a) Shukla, B.; Visen, P.K.S.; Patnaik, G.K.; Tripathi, S.C.; Srimal, R.C.; Dayal, R.; Dobhal, P.C.; *Phytochemistry Res.*, **1992**, *6*, 74. b) Male Sprague-Dawley rats (100-125 g) were caged separately in groups of 5 animals each. Group I consists of normal animals. Group II animals were administered thioacetamide (200 mg/kg, p.o. x 1 day). Group III animals were fed the test compound daily at a dose level of 6 mg/kg (p.o. x 7 days). Thioacetamide was administered to them on day 7.
Animals of all the groups were sacrificed 24 h after administration of the toxin and their blood collected. Serum enzyme parameters, described in Table 1, were analysed by standard procedures and the % protection was calculated using the formula :

$$\frac{\text{(Toxin treated) - (Toxin + test compound treated)}}{\text{Normal - (Toxin treated)}} \times 100$$

(*Received in Japan* 9 *September* 1997; *accepted* 6 *November* 1997)