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FUNCTIONALIZED 1,3-TERARYLS AS A NEW CLASS OF HEPATOPROTECTANTS#: PART V

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Abstract: Functionalized 1,3-teraryls, synthesized through ring transformation of 6-aryl-3-carbomethoxy-4-methylthio-2H-pyran-2-one from arylketone have been screened for their hepatoprotective activity and some of them have demonstrated significant protection in animal model.

Introduction : Wide prevalence of liver diseases and lack of hepatoprotective agents necessitated to develop satisfactory remedies for its protection. Except herbal preparations which support or promote the process of healing or regeneration of liver cells, no synthetic drug is available in the clinic for the treatment of hepatic ailments. The remedies available in the modern system of medicine provide only symptomatic relief without affecting the disease process and their use is normally associated with the risk of relapse and dire side effects.

Various phenols, thioethers and esters either from natural or synthetic origin have demonstrated choleretic and hepatoprotective activities[1] in animal models. By virtue of radical scavenging property[2-4] of sulfur compounds, numerous thioethers have been synthesized and reported for their potent hepatoprotective activity. Based on the knowledge and structural informations available from natural products, 1,3-teraryls with thioether and ester substituents in the central aromatic ring were designed. The electron donating and withdrawing substituents were also introduced alternatively into the first and third aromatic rings of 1,3-teraryls to assess the effect of functional groups on hepatoprotective activity.

Our approach to synthesize 1,3-teraryls is based on the base induced ring transformation[5] of 6-aryl-3-carbomethoxy-4-methylthio-2H-pyran-2-ones (**2**) from aryl ketones. The position C-6 in lactone **2** is most susceptible to nucleophile among other electrophilic centres. The carbanion generated from aromatic ketone *in situ* by alkali attacks at C-6 position followed by ring opening, decarboxylation and intramolecular cyclization. Initially symmetrical 1,3-teraryls (**3**) were obtained directly from the reaction of ketene dithioacetal (**1**) and aromatic ketone as a minor and 6-aryl-3-

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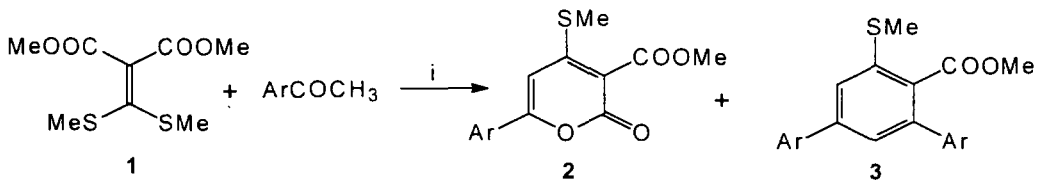
carbomethoxy-4-methylthio-2H-pyran-2-one (**2**) as a major products. Unsymmetrical 1,3-teraryls (**4**) were synthesized from the reaction of **2** and aromatic ketones. All the compounds (Scheme 1) were characterized by elemental and spectroscopic analyses.

Scheme 1 :



4	Ar	Ar'
a	4-ClC_6H_4	4-FC_6H_4
b	4-ClC_6H_4	4-BrC_6H_4
c	4-ClC_6H_4	3,4-$Cl_2C_6H_3$
d	4-FC_6H_4	3,4-$Cl_2C_6H_3$
e	4-ClC_6H_4	4-$NO_2C_6H_4$
f	4-ClC_6H_4	3-$NO_2C_6H_4$
g	4-FC_6H_4	3-$NO_2C_6H_4$
h	3-Cl-4-FC_6H_3	3-$NO_2C_6H_4$

3	Ar
a	4-FC_6H_4
b	4-ClC_6H_4
c	4-BrC_6H_4

Reagents / Conditions: i) DMF/KOH/RT ii) Ar'$COCH_3$/DMF/KOH/RT

Most of the synthesized compounds were evaluated for their hepatoprotective activity in thioacetamide induced hepatic injury in rats as reported earlier[6-8] The activity of the compounds was assessed on the basis of % protection afforded in various levels of serum enzyme parameters such as glutamate pyruvate transaminase (GPT), glutamate oxaloacetate transaminase (GOT) and alkaline phosphatase (ALP). The activity profile of screened compounds is presented in Table 1.

The serum enzyme profile of the screened compounds (**3a-c, 4a-h**) to the standard drug revealed that compound **4f** is most active and gave significant protection in all the parameters compared to silymarin. The other two compounds **4c** and **4d** have demonstrated better or equivalent efficacy in most of the parameters than standard drug used in this study.

Table 1: Hepatoprotective activity of compounds of prototype **3** and **4** against thioacetamide induced toxicity in rats at 10 mg/kg dose (p.o. x 7 days). Values in parenthesis are the % protection afforded by the test compounds in serum enzyme parameters.

Group/Compound No.	GOT (U/L)	GPT (U/L)	ALP (U/L)
Normal (I)	101.6±8.98	95.9±8.65	102.4±12.59
TA treated (II)	235.8±3.16***	407.6±9.83***	349.1±3.93***
Compound+TA treated (III)			
3a	229.1±4.18(5)	370.2±5.35(12)	341.2±9.22(3)
3b	186.3±5.02(37)	248.5±4.64**(51)	268.2±4.84***(33)
3c	202.1±5.96(25)	295.4±8.77*(36)	324.2±7.27(10)
4a	222.3±8.01(10)	392.3±3.21(5)	334.2±7.02(6)
4b	208.3±7.99(20)	361.5±6.81(15)	330.2±9.71(8)
4c	147.3±3.57***(66)	258.1±3.09**(49)	245.1±5.21**(42)
4d	159.3±4.83**(57)	186.3±4.41***(71)	235.5±3.46***(46)
4e	229.4±8.29(5)	270.4±2.19*(44)	289.9±3.15**(24)
4f	149.9±3.32***(64)	190.1±6.91***(70)	203.6±5.61***(60)
4g	208.9±8.77(20)	360.1±7.71(15)	307.2±6.32(17)
4h	211.6±2.71(18)	370.2±8.23(12)	304.1±5.38(18)
Silymarin (Standard drug)	150.2±3.29***(64)	217.9±4.34***(61)	220.1±7.29***(52)

Values are mean±S.D. of six rats in each group. Group II compared with group I (***P < 0.001), group III compared with group II (**P < 0.01, *P < 0.05). Analysis of varianu (ANOVA) was done for significance. Individual comparision within the group was carried out by Student's 't' test.

The topographical study of the compound **3** and **4** revealed that all of them (**3a-c, 4a-h**) possess 4-carbomethoxy and 5-methylthio substituents in their molecular makeup. The only difference lies in the nature and position of the substituent in the aromatic rings attached at 1 and 3 positions of the central ring. It is evident from the activity profile that compounds with 4-fluorophenyl or 4-chlorophenyl substituent at position 1 and 3,4-dichlorophenyl or 3-nitrophenyl

substituent at position 3 contributed significantly to the hepatoprotective activity. A drastic reduction in efficacy for GPT and ALP was observed when 3-nitrophenyl group in **4f** was exchanged by 4-nitrophenyl (**4e**). Presence of highly electronegative substituent in phenyl ring at position 1 without altering aryl substituent at position 3 of the central ring in **4g,h** reduced the hepatoprotective activity. Among symmetrical 1,3-teraryls only compounds with high electronegative substituent in 1,3-phenyl ring in **3b** demonstrated better activity than **3a** and **3c**.

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