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TETRAAZAACENAPHTHENE AND TETRAAZAPHENALENE DERIVATIVES: A NEW CLASS OF HEPATOPROTECTANTS: PART IV

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Abstract: The synthesis and hepatoprotective activity of imidazolidine **(3a)**, hexahydropyrimidine **(3b)**, imidazo[3,2-c]pyrimidine **(5)**, tetraazaacenaphthene **(4a-d)** and tetraazaphenalene **(4e)** derivatives are described. Some of the screened compounds have shown a very significant activity.

The liver plays a pivotal role in the maintenance of metabolic homeostasis and its perpetual exposure to exogenous toxins and therapeutic agents leads to metabolic derangements. In addition to its role in metabolism of therapeutic agents, it is also responsible for inactivation or modification of several endogenous hormones whose imbalance impair the hepatic secretory activity. However, a minor impairment manifests variety of defects and its severity depends upon the extent of initial insult.

Except herbal preparations, no synthetic drug is so far designed and available for the treatment of hepatic damage. However, immunosuppressant and corticosteroids are in clinical use for the treatment of hepatic damage but they only provide symptomatic relief with severe side effects and chances of relapse. In presence of excessive amount of free radicals, the glutathione levels of hepatocytes are readily depleted leading inactivation of cellular proteins and wide spread hepatocellular necrosis. Hence, the importance of radical quencher as chemotherapeutic agents was realised. The property of nitrogen and sulfur compounds as radical quencher aroused considerable interest to design and synthesize N,S-heterocycles as potential hepatoprotectants.

The radical scavenging property[1-3] of oxo and thio imidazole and fused pyrimidine derivatives aroused considerable interest to synthesize ethyl (imidazolidin-2-ylidene) cyanoacetate **(2a)**, dimethyl (imidazolidin-2-ylidene) malonate **(2c)**, ethyl (hexahydropyrimidin-2-ylidene) cyanoacetate **(2b)** and dimethyl (hexahydropyrimidin-2-ylidene) malonate **(2d)** by the reaction[4,5] of ketene dithioacetal **(1a,b)** with 1,2-diaminoethane and 1,3-diaminopropane[6,7] separately. The acid catalysed cyclization of **2a,b** with thiosemicarbazide by exploiting cyano function yielded imidazolidine derivatives **(3a,b)**. Heataing of **2a-d** with neat alkyl/aryl isocyanate or isothiocyanate separately provided tetraazaacenaphthene[8] **(4a-d)** and tetraazaphenalene **(4e)** derivatives. In case of reaction of **2a** with ethyl isothiocyanate an uncyclized product **5** was also isolated. All the compounds (Scheme 1) were characterized[9] by elemental and spectroscopic analyses. Only compounds of the prototypes **3-5** were evaluated for hepatoprotective activity against thioacetamide-induced hepatic damage as reported earlier[10-12].

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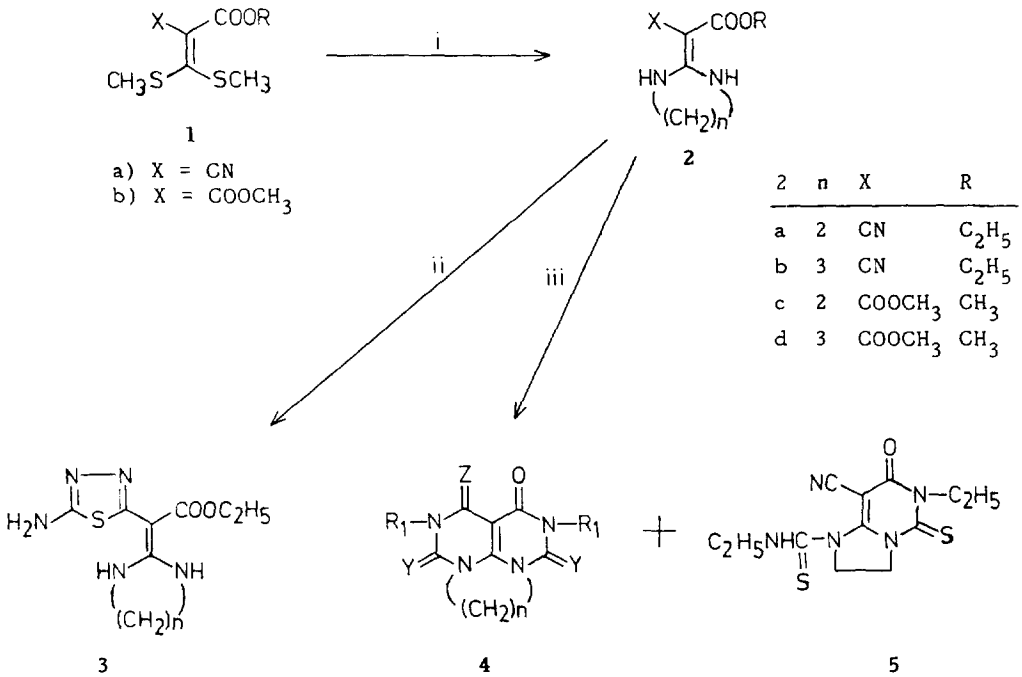
The activity of the compounds was assessed on the basis of % protection afforded in various levels of serum enzyme parameters such as glutamate pyruvate transaminase (GPT), glutamate oxaloacetate transaminase (GOT), alkaline phosphatase (ALP) and bilirubin. The screening results are presented in Table 1.

Scheme 1



4	n	Y	Z	R_1
a	2	S	O	C_2H_5
b	2	S	O	C_6H_5
c	2	O	O	2-$CH_3C_6H_4$
d	2	S	NH	C_2H_5
e	3	S	NH	C_2H_5

Reagents/Conditions: i) $NH_2(CH_2)_nNH_2/C_2H_5OH/110°C$, ii) $NH_2C(S)NHNH_2$/TFA/60-80°C, iii) $R_1NCY/160°C$.

Table 1: Hepatoprotective activity of compounds of prototypes **3a,b, 4a-e** and **5** against thioacetamide-induced toxicity in rats at 6 mg/kg dose (P.O. x 7 days). Values are the % protection afforded by the compounds in serum enzyme parameters.

Prototype	GOT	GPT	ALP	Bilirubin
3a	33	51	19	53
3b	26	50	38	22
4a	20	34	22	31
4b	27	18	20	25
4c	18	15	16	18
4d	50	87	17	57
4e	40	50	48	50
5	31	70	56	60
Silymarin (standard drug)	50	47	47	61

A comparative study of serum enzyme parameters and bilirubin for the compounds **3a,b, 4a-e** and **5** to the standard drug revealed that among all the screened compounds **4d** and **5** were found more effective than silymarin in most of the parameters. In general compounds possessing imino functionality **(4d,e)** and uncyclized product **(5)** displayed better efficacy than corresponding oxo analogs **(4a,b)**. The protective property of 3,5,6,8-tetraoxo analog **(4c)** was considerably attenuated. This study provided new prototype structures displaying significant hepatoprotective activity and opens a new avenue for further exploration.

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References and Notes:

1. Ames, B.N.; Cathcart, R.; Schwiers, E.; Hochstein, P.; Proc. Natn. Acad. Sci. U.S.A., **1981**, 78, 4858.
2. Garbutt, G.J.; Smith, R.C.; Fedn. Proc., **1980**, 39, 1879.
3. Smith, R.C.; Reeves, J.C.; Dage, R.C.; Schnettler, R.A.; Biochemical Pharmacology, **1987**, 36, 1457.
4. Gompper, R.; Töpfl, W.; Chem. Ber., **1962**, 95, 2871.
5. Sasho, S.; Obase, H.; Ichikawa, S.; Yoshizaki, R.; Bioorg. Med. Chem. Letters, **1994**, 4, 615.
6. Neidlein, R.; Kikelj, D.; Kramer, W.; J. Heterocyclic Chem., **1989**, 26, 1335.
7. Huang, Z.-T.; Wang, M.-X.; J. Chem. Soc., **1993**, 1085.
8. Wamhoff, H.; Lamers, L.; Synthesis, **1993**, 111.

9. Spectroscopic data for the representative compounds: **3a**: yield 73%; m.p. 245°C; MS m/z 255 (M^+), 210 (M^+-OC_2H_5), 182 (M^+-$COOC_2H_5$); IR(KBr) 1680 (CO), 3110 (NH) 3320 (NH), 3440 (NH_2) cm^{-1}; ^1H NMR (DMSO-d_6) δ 1.24 (t, 3H), 3.6 (t, 4H), 4.22 (q, 2H), 7.8 (s, 2H). **3b**: yield 79%; m.p. 180°C; MS m/z 269 (M^+), 196 (M^+-$COOC_2H_5$); IR(KBr) 1650 (CO), 3180 (NH), 3400 (NH_2) cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.35 (t, 3H), 1.98 (m, 2H), 3.4 (m, 4H), 4.22 (q, 2H). **4a**: yield 87.6%; m.p. > 260°c; MS m/z 310 (M^+); IR(KBr) 1660 (CO) cm^{-1}; ^1H NMR (DMSO-d_6) δ 1.28 (t, 6H), 4.46-4.52 (m, 8H). **4b**: yield 78%; m.p. >260°C; MS m/z 406 (M^+); IR(KBr) 1650 (CO) cm^{-1}; ^1H NMR (DMSO-d_6) δ 4.4 (s, 4H), 7.20 (d, J=8.84 Hz, 4H), 7.4-7.5 (m, 6H). **4c**: yield 72.5%; m.p. 245°C; MS m/z 402 (M^+); IR (KBr) 1660 (CO), 1710 (CO) cm^{-1}; ^1H NMR (DMSO-d_6) δ 2.28 (s, 6H), 3.4 (s, 4H), 7.0-7.16 (m, 4H), 7.8 (d, J=8.16 Hz, 2H), 8.22 (d, J=8.2Hz, 2H). **4d**: yield 51%; m.p. 218°C; MS m/z 309 (M^+), 281 (M^+-C_2H_4); IR(KBr) 1670 (CO), 3260 (NH) cm^{-1}; ^1H NMR (DMSO-d_6) δ 1.18 (t, 6H), 4.25 (s, 4H), 4.35 (q, 2H), 4.52 (q, 2H). **4e**: yield 63%; m.p. 210°C; MS m/z 323 (M^+); IR(KBr) 1650 (CO), 3240 (NH) cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.3 (t, 6H), 1.98 (m, 2H), 4.0-4.2 (q, 4H), 4.5 (t, 2H), 4.7 (t, 2H). **5**: yield 43%; m.p. > 280°C; MS m/z 309 (M^+), 280 (M^+-C_2H_5); IR(KBr) 1664 (CO), 2282 (CN), 3288 (NH) cm^{-1}; ^1H NMR (DMSO-d_6) δ1.2 (t, 6H), 3.86 (t, 2H), 4.3 (t, 2H), 4.42 (q, 2H), 4.58 (q, 2H).
10. Ram, V.J.; Haque, N.; Singh, S.K.; Nath, M.; Shoeb; A.; Tripathi, S.C.; Patnaik, G.K.; Bioorg. Med. Chem. Letters, **1994**, 4, 1453.
11. Ram, V.J.; Nath, M.; Patnaik, G.K.; Bioorg. Med. Chem. Letters, **1995**, 5, 695.
12. Shukla, B.; Visen, P.K.S.; Patnaik, G.K.; Tripathi, S.C.; Srimal, R.C.; Dayal, R.; Dobhal, P.C.; Phytotherapy Res., **1992**, 6, 74.

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