(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
18 October 2007 (18.10.2007)

PCT

(10) International Publication Number
WO 2007/116412 A1

(51) International Patent Classification:
*C07D 239/54* (2006.01) *A61K 8/49* (2006.01)
*C07D 239/60* (2006.01)

(21) International Application Number:
PCT/IL2007/000471

(22) International Filing Date: 11 April 2007 (11.04.2007)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
60/790,807 11 April 2006 (11.04.2006) US

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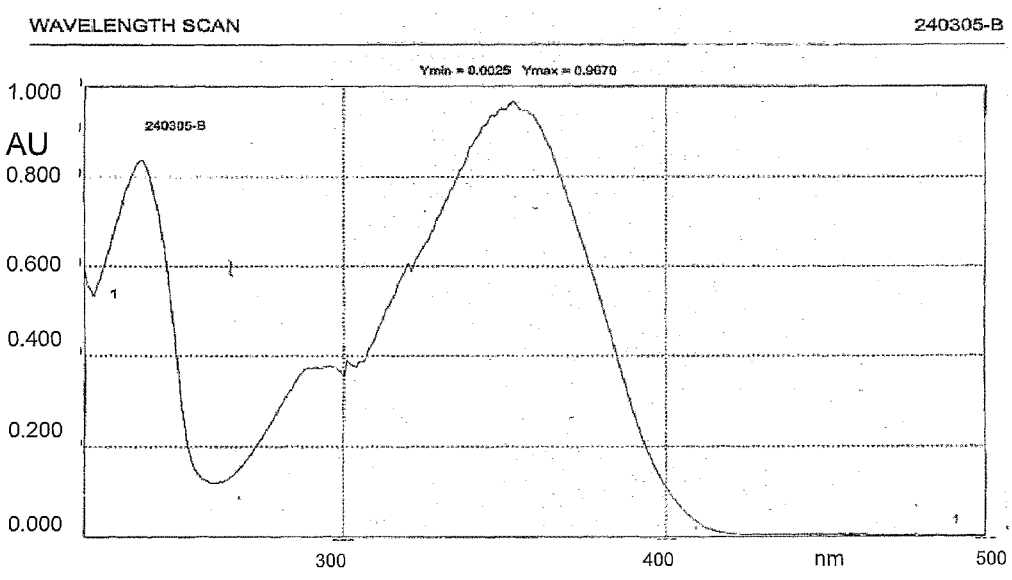
(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, SV, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, LV, MC, MT, NL, PL, PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

**Published:**
— *with international search report*
— *before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments*

*For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.*

(54) **Title:** SUBSTITUTED PYRIMIDINES, PROCESS FOR THEIR PRODUCTION AND THEIR USE AS EFFECTIVE ABSORBENTS OF UV IRRADIATION




(57) **Abstract:** The present invention discloses substituted pyrimidines, processes for their synthesis and their use as effective sun-protecting agents either alone or in combination with other known sun-protecting agents.

WO 2007/116412 A1

# SUBSTITUTED PYRIMIDINES, PROCESS FOR THEIR PRODUCTION AND THEIR USE AS EFFECTIVE ABSORBENTS OF UV IRRADIATION

## FIELD OF THE INVENTION

The invention relates to novel substituted pyrimidines, processes for their synthesis and their use as ultraviolet-absorbing agents.

## BACKGROUND OF THE INVENTION

Exposure to ultraviolet radiation (UVR) from the sun plays a causal role in acute and chronic skin damage such as sunburn, skin cancer, immunosuppression, and photoaging of the skin. These consequences of sun exposure are attracting considerable attention due to an alarming increase in the incidence of sun-related skin cancers. Major culprits of increased sun-related morbidity include changes in life style with more time spent in outdoor recreational activities resulting in significant augmentation in the amount of UVR received and depletion of stratospheric ozone, which is the Earth's protection layer against hazardous radiation. To amend for these dangerous developments, a sun avoidance strategy has been advocated in which the topical application of sunscreens constitutes a cornerstone. However, the increased use of sunscreens raises several concerns: Most sunscreens do not effectively filter out all the detrimental wavelengths of sun light. Second, even though sunscreens prevent sunburn, little is known regarding the threshold or dose-response for UVR-induced effects on other endpoints such as immune suppression and DNA damage. Finally, there is increasing body of evidence that presently used topical sunscreens might undergo UV-induced photooxidation and form potentially toxic metabolites.

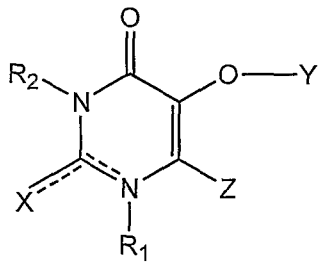
Search for a new generation of sunscreens stems from the various drawbacks the present sunscreen agents possess, including photo- and nonphotoinduced skin sensitivity and photogenotoxicity. Naturally occurring UV filters in the form of pigments are abundant and might constitute attractive candidates for new effective and nontoxic sunscreens. In addition to melanin and flavonoides, they include scytonemins found in cyanobacteria with a recently elucidated structure (Proteau et al (1993) Experimentia 49:825-829). This pigment, the first shown to be an effective photostable UV shield in

prokaryotes, is a dimeric molecule of indole and phenol subunits. The scytonemin absorbs strongly and broadly in the spectral region of 325-425 nm (UVA) but also has an absorption in the UVB (280-320 nm) and UVC (<250 nm) regions (US patent No. 5,461,070). Mycosporine is another family of water-soluble, ultra violet-absorbing metabolites found in cyanobacteria with an UV absorption peak in the UVB range. The elucidated structure of mycosporine is cyclohexenone chromophore conjugated with the nitrogen of an amino acid or an amino alcohol. A variety of specific mycosporin amino acids were identified and their distribution in various groups has been described (Karentz et al. (1991) Marine Biology 108, 157-166).

## SUMMARY OF THE INVENTION

The present invention is based on the findings of a novel family of substituted pyrimidines that can absorb ultra violet radiation.

Thus the present invention is directed to a compound of formula (I):



(I)

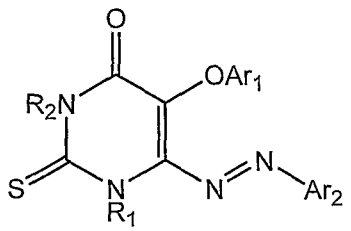
wherein ------ denotes an optional double bond, where one of the two optional double bonds being a double bond and the other a single bond; $R_1$ is null, hydrogen or $C_{1-6}$alkyl which may be optionally substituted with halogen; $R_2$ is hydrogen or $C_{1-6}$alkyl which may be optionally substituted with halogen; X is hydrogen, $C_{1-4}$alkyl, S-$CH_3$, SH or =S; Y is hydrogen, optionally substituted tetrahydropyran, tetrahydrothiopyran, dithiane, or an optionally substituted aryl or heteroaryl; and Z is (a) $NH_2$; (b) hydrogen (c) -N=NAr, Ar being optionally substituted aryl group.

$C_{1-6}$alkyl is branched or straight chain alkyl groups and may be methyl, ethyl, propyl, isopropyl, butyl, secbutyl, tertbutyl, pentyl, neopentyl, or hexyl. $C_{1-4}$alkyl may be methyl, ethyl, propyl, isopropyl, butyl, secbutyl or tertbutyl that may be partially halogenated, the halogen selected from fluorine, chlorine, bromine, iodine.

Substituents are halogens, straight or branched $C_{1-6}$alkyl groups optionally partially halogentated. Halogens are selected from fluorine, chlorine, bromine, iodine.

Heteroaryl is a 5- or 6-membered aromatic ring containing one or two heteroatoms selected from O, N or S. In particular, it may be furan, pyrrole, thiophene, imidazole, pyrazole, pyridine, pyrimidine, pyrazine.

In one embodiment, the present invention is directed to a thia-aza- pyrimidine of formula (II):

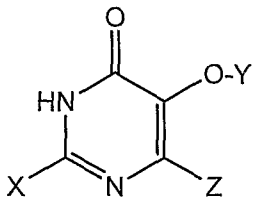



(II)

wherein $R_1$ and $R_2$ are independently selected from hydrogen or $C_{1-6}$alkyl that may be optionally substituted with halogen; $Ar_1$ is selected from the group consisting of optionally substituted tetrahydropyran, tetrahydrothiopyran, dithiane, aryl or heteroaryl; $Ar_2$ is an optionally substituted aryl group.

Preferably, $R_1$ and $R_2$ are the same or different and are hydrogen or $C_{1-6}$alkyl, optionally substituted by halogen; and $Ar_1$ and $Ar_2$ may be the same or different and are an aryl group optionally substituted with one or two $C_{1-6}$alkyl groups. More preferably, $R_1$ and $R_2$ are hydrogen and $Ar_1$ and $Ar_2$ are an aryl group independently optionally substituted with one or two $C_{1-6}$alkyl groups.

In a further embodiment, the present invention is directed to a compound of formula (III):

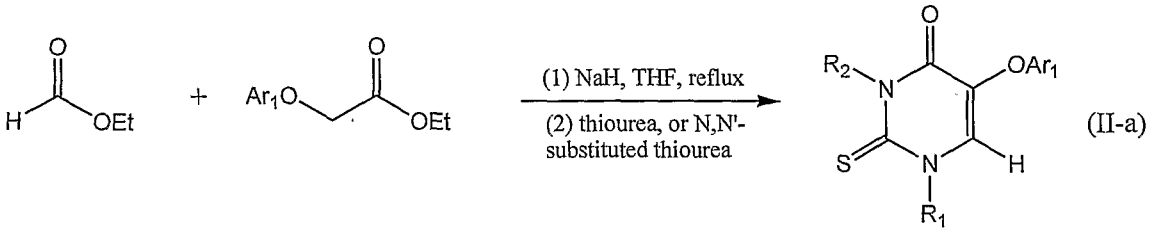



(III)

wherein X is hydrogen, $C_{1-4}$alkyl, S-$CH_3$, SH; Z is (a) $NH_2$; (b) hydrogen (c) -N=N-Ar, Ar being an optionally substituted aryl group; Y is hydrogen, optionally substituted tetrahydropyran or aryl. Preferably, Y is hydrogen, X is hydrogen, $C_{1-4}$alkyl, S-$CH_3$ or SH; and Z is $NH_2$.

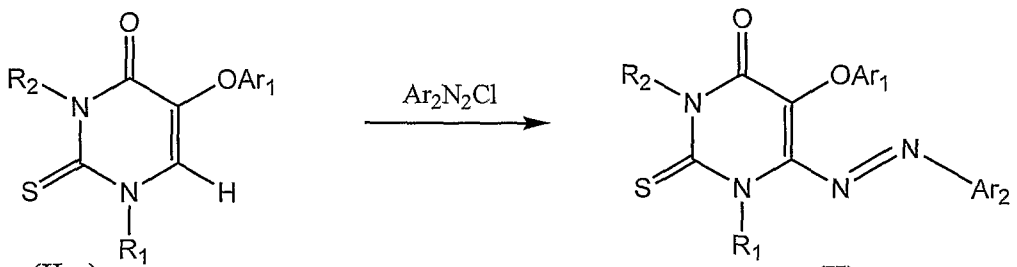
The invention is further directed to a process for synthesizing a compound of formula (II), comprising:

(a) reacting formic ethyl formate with α-aryloxy-acetic acid ethylester in the presence of a base and thiourea or N,N'-substituted thiourea to yield an optionally substituted thia-pyrimidine of formula (II-a), according to the following reaction scheme:




(II-a)

(b) reacting the optionally substituted thia-pyrimidine of formula (II-a) with aryldiazonium chloride, the aryl group being optionally substituted, to yield the thia-aza-pyrimidine of formula (II), according to the following reaction scheme:

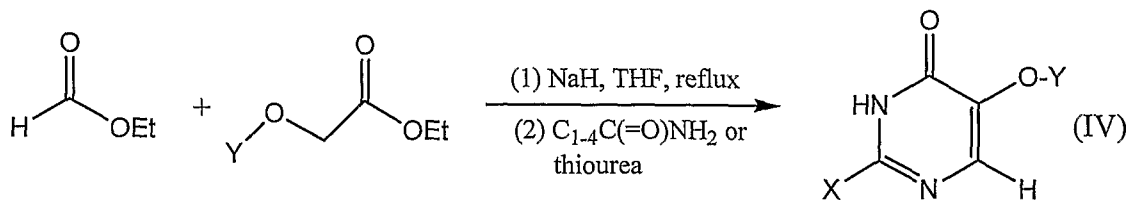



(II-a) (II)

wherein $R_1$, $R_2$, $Ar_1$ and $Ar_2$ are as defined above. Substituted thiourea is a thiourea substituted by one or two $C_{1-6}$alkyl groups that may be optionally substituted with halogen.

The invention is further directed to a process for the manufacture of a pyrimidine of formula (III-a), comprising:

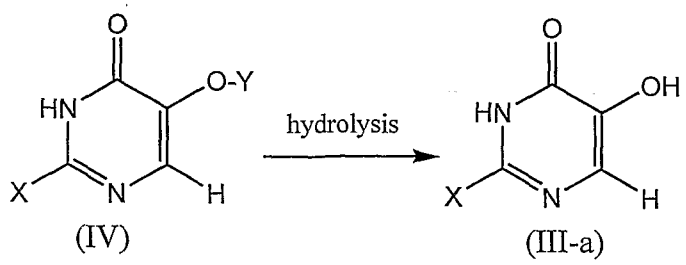
(a) reacting ethyl formate and the ethylester of the appropriate α-oxy acetic acid derivative in the presence of sodium hydride and $C_{1-4}C(=O)NH_2$ or thiourea to yield a compound of formula (IV), according to the following reaction scheme:




(IV)

wherein X is $CH_3$ or SH and Y hydrogen, optionally substituted tetrahydropyran or aryl;

(b) hydrolyzing a compound of formula (IV) to yield a compound of formula (III-a), according to the following reaction scheme:

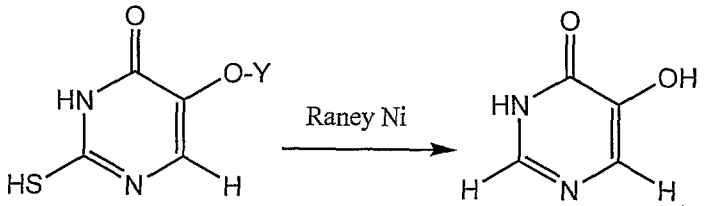



(IV) (III-a)

wherein X is $C_{1-4}$ or SH.

The invention is further directed to a process for the manufacture of a pyrimidine of formula (III-b), comprising:

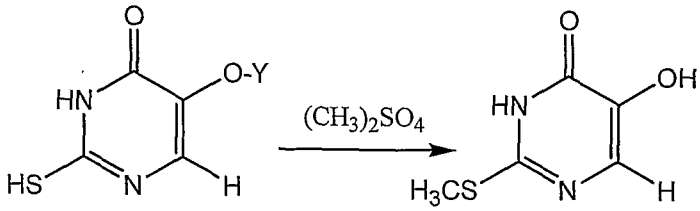
reacting a compound of formula III-a as defined above, wherein X is SH; with Raney Ni to yield a compound of formula (III-b) according to the following reaction scheme:




(III-a) (III-b)

The invention is further directed to a process for the manufacture of a pyrimidine of formula (III-c), wherein X is $SCH_3$, Y and Z are hydrogen, comprising:

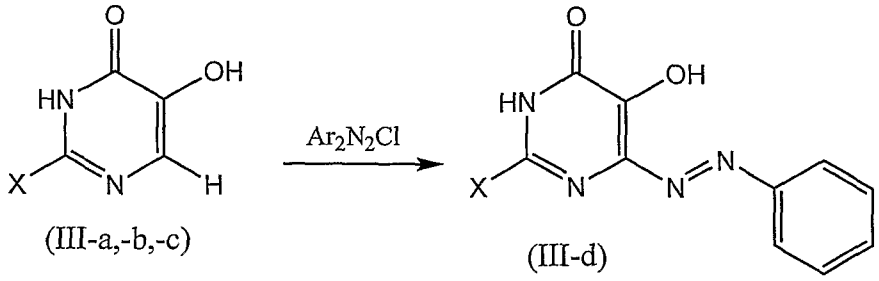
reacting a compound of formula (III-a) of claim 7 wherein X is SH with $(CH_3)_2SO_4$ to yield a compound of formula (III-c) according to the following reaction scheme:




(III-a) (III-c)

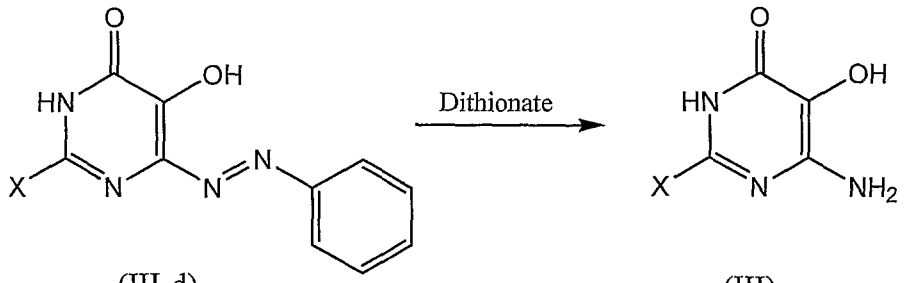
The invention is further directed to a process for the manufacture of a compound of formula (III-d) wherein X is hydrogen, SH, $SCH_3$ or $C_{1-4}$, Y is H and Z is $-N{=}NAr_2$ comprising:

reacting any one of compounds of formulae (III-a), (III-b), (III-c) with a diazotizing reagent of formula $-N{=}NAr_2$ $Ar_2$ as defined above, according to the following reaction scheme:




(III-a,-b,-c) (III-d)

The invention is further directed to a process for the manufacture of a compound of formula III, wherein X is hydrogen, SH, $SCH_3$ or $C_{1-4}$, Y is hydrogen and Z is $NH_2$, comprising reacting a compound of formula III-d with dithionate according to the following reaction scheme:




(III-d) (III)

Compounds of formulae III-a. III-b, III-c or III-d or the compound of formula III wherein X is hydrogen, SH, $SCH_3$ or $C_{1-4}$, Y is hydrogen and Z is $NH_2$ being novel are also being part of the present invention.

The invention further relates to topical formulations providing protection for skin from the hazardous effects of ultra violet irradiation, in particular, UVA and UVB irradiation, comprising an effective amount of a compound of formulae I-III together with suitable adjuvants. Such topical formulations may further comprise at least one additional sun-protecting agent. The additional sun-protecting agent may be selected from the group consisting of organic or inorganic sun protecting agent. Non limiting examples of the at least one additional sun protecting agent are derivatives of anthranilates, benzophenones, camphors, cinnamates, dibenzoylmethanes, p–aminobenzoates, salicylates, zinc oxide, titanium dioxide and mixtures thereof

The invention still further relates to the use of an effective amount of a compound of formulae I-III, optionally together with at least one additional sun-protecting agent for the preparation of a sunscreen formulation providing protection from ultra violet irradiation, in particular, UVA and UVB irradiation.

## BRIEF DESCRIPTION OF THE DRAWINGS

In order to understand the invention and to see how it may be carried out in practice, embodiments will now be described, by way of non-limiting example only, with reference to the accompanying drawings, in which:

**Fig. 1** depicts two prior art molecules used in comparison experiments reported herein.

**Fig. 2** depicts Hammett correlations: Initial rate of dissociation *vs.* $\sigma_p$ (filled squares) and $\sigma_p^+$ (empty squares) for the autoxidation of compounds **8a-e** in air saturated solutions at pH 7.0 and 25°C. $\rho$ value for $\sigma_p$ is –2.40, $r^2$=0.5868, $\rho$ value for $\sigma_p^+$ is –1.28, $r^2$=0.949.

**Fig. 3** depicts the Ultra violet spectrum of a compound of formula (II).

## DETAILED DESCRIPTION OF EMBODIMENTS

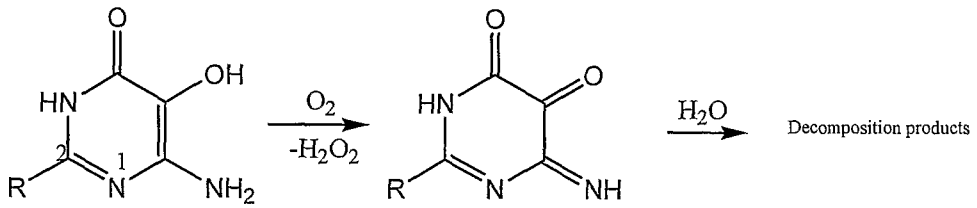
As mentioned above, the present invention is directed to new pyrimidine derivatives possessing unique structural features of enol-amines similar to those found in amino reductones and further having unique ultra violet absorption characteristics. Several amino reductones occur naturally and are responsible for life-threatening hemolytic episodes in favism. On the other hand, amino reductones may also be useful sunscreens (sun-protecting agents). The amino reductone structure *i.e.*, enolamine, occurs in a number of natural products. For instance, several species of ancient organisms (fungi, cyanobacteria and lichens) produce UV absorbing metabolites such as MAA's (mycosporine like amino acids, **Figure 1**) that are characterized by a cyclohexenone **1** or cyclohexenimine **2** chromophore conjugated with the nitrogen substituent of an amino acid or its imino alcohol and having absorption maxima ranging from 310 to 360 nm.

MAA's can be considered as potential sun-protecting agents as their conjugated amino enolic chromophore has both broad absorption in the UV region, and antioxidant properties desirable in a sun blocker. Certain pyrimidine derivatives, i.e., isouramil (6-amino-2,5-dihydroxypyrimidin-4-one; $A_d$ in Scheme 1) and divicine (2,6-diamino-5-hydroxypyrimidin-4-one; Ae in scheme 1) incorporate the amino reductone group. They are found in beans as glycosides and are thought to be the causative agents in favism. A synergistic cytotoxicity has been demonstrated between carboplatin and divicine on murine erythroleukemic cells. Divicine also enhances *in-vitro* and *in-vivo* lipopolysaccharide-induced release of tumor necrosis factor (TNF).

In accordance with the present invention there exists a marked dependency of the autoxidation rate of five pyrimidine derivatives **8a-e** (Scheme 1) on the electron releasing power of the substituent at C2 leading to a route for controlling the oxidation rate of such compounds in their use, in particular as sun screening agents. In order to examine their stability, kinetic studies of their auto-oxidation were carried, in particular in comparison to other known amine reductones.

Compounds **8a-c,** of the present invention differ from isouramil (8d) and divicine (8e) only at C2. All five compounds were subjected to autoxidation under neutral conditions giving presumably $H_2O_2$ as shown in the following Scheme 1:

**Scheme 1**: Pyrimidine derivative oxidation




A B

**8a: R=$CH_3$; 8b: R=H; 8c: R=$SCH_3$; 8d: R=OH (isouramil); 8e: R=$NH_2$ (divicine).**

The autoxidation rate was measured in air-saturated buffer phosphate solutions 0.05 M at pH 7 and 25°C. The solutions contained 1 mM EDTA to minimize catalysis of the oxidation by trace metallic cations. The rate of autoxidation was measured spectrophotometrically by following the decrease of the UV absorbance of the pyrimidines at their respective λ max (Table 1).

**Table 1.** Spectral properties and initial autoxidation rates for compounds **Aa-e.**

| Substituent R | $\lambda_{max}$ nm (ε) | Initial rate μM/sec | $\sigma_p$[a] | $\sigma_p^+$[a] |
|---|---|---|---|---|
| H | 274 (13000)[b] | 0.00087[c] | 0 | 0 |
| $CH_3$ | 275 (16200)[b] | 0.0015[c] | -0.17 | -0.31 |
| $SCH_3$ | 286 (10800)[b] | 0.0097[c] | 0 | -0.6 |

| | | | | |
|---|---|---|---|---|
| OH | 280 (14100)[d] | 0.067[e] | -0.37 | -1.6[f] |
| $NH_2$ | 285 (9800)[d] | 0.061[e] | -0.66 | -1.3 |

[a] Cookell, S. C. (1998). Ultraviolet radiation, evolution and the π-electron system. *Biological Journal of the Linnean Society,* 63, 449- 457. [b]This work. [c]This work; air saturated 0.05M phosphate buffer pH=7.0, 1mM EDTA, 25 °C, [Pyrimidine]= $2.4x10^{-5}$ M. reference. [e]Calculated from (Sinha, R.P., Klisch, M., Grongier, M & Hader, D.P. (1998). Ultra violet-absorbing/ screening substances in cyanobacteria, phytoplankton and macroalgae. J .*Photochem. Photobiol. B:Biol.,* **47**,83-94) see text. [f]$\sigma_p^+$ for OH from (R.P. Sinha, N.K. Ambasht, J.P. Sinha, M. Klisch and D.P. Häder. UV-B-induced synthesis of mycosporine-like amino acids in three strains of *Nodularia* (cyanobacteria), *J. Photochem. Photobiol. B: Biol.,* 2003, 71, 51-5).

All three compounds 8**a-c** of the present invention showed much slower oxidation rates compared with isouramil and divicine. This is probably the reason why there was no transient appearance of an absorption maximum around 240-255 nm which is assumed to be due to the intermediacy of oxidized pyrimidine **B (Scheme 1)**, and was found in the autoxidation of isouramil, divicine and related systems. The decrease in the absorbance of **8a-c**, followed a reasonably pseudo first order reaction in the pyrimidine concentration (the dissolved oxygen concentration was at least 13 times higher). However, it was found (Winterbourn, C.C.; Cowden, W.B.; Sutton, H. *Biochem. Pharmacol.* **1989,** *38,* 611-618) that the reaction mechanism is complex and involves radical intermediates and chain reactions and that the dependency on the pyrimidine concentration is far from simple. Therefore, in accordance with the present invention a different approach was adapted that uses the measured initial reaction rates for checking the quantitative dependency of the oxidation rate on the electron releasing power of the substituent in the C2 position. The results for compounds **8a-c** of the present invention are summarized in Table 1. Table 1 also contains the initial rates for the reactions of isouramil and divicine (**8d** and **8e**) calculated from Winterbourn, C.C.; Cowden, W.B.; Sutton, H. *Biochem. Pharmacol.* **1989,** *38,* 611-618; (aerated 0.05M phosphate buffer, pH 7, 23°C, 50mM DTPA and similar to our pyrimidine concentrations) using ΔH of 60.2 kJ/mole (Chevion et al.[5a] ). A plot of the logarithmic values of the initial rates against Hammett $\sigma_p$ constants did not give a reasonable correlation. However, the correlation was greatly improved upon use of $\sigma_p^+$ values, ρ value is –1.28 ($r^2$=0.949) (**Figure 2**).

The following complex chain mechanism (Scheme 2) was suggested (Winterbourn, C.C.; Cowden, W.B.; Sutton, H. *Biochem. Pharmacol.* **1989,** *38,* 611-618; Winterbourn, C.C.; Munday, R. *Free Rad. Res. Commun.* **1990,** *8,* 287-293) to account for the autoxidation rates of isouramil and divicine. $DH_2$ stands for the reduced pyrimidine, $DH^{\cdot}$ for the pyrimidine radical (probably structure **10**) and D for the oxidized pyrimidine, most probably having structure **B** (Scheme 1). It is reasonable to expect the same mechanism for the compounds **8a**, **8b** and **8c** (Scheme 1) of the present invention.

**Scheme 2.**

(1) $DH_2 + O_2 \longrightarrow O_2^{\bullet-} + DH^{\bullet} + H^+$

(2) $DH_2 + H^+ + O_2^{\bullet-} \longrightarrow DH^{\bullet} + H_2O_2$

(3) $DH^{\bullet} + O_2 \rightleftharpoons D + O_2^{\bullet-} + H^+$

(4) $DH_2 + D \rightleftharpoons 2DH^{\bullet}$

(5) $2O_2^{\bullet-} + 2H^+ \longrightarrow H_2O_2 + O_2$

The observed initial reaction rates must be the result of a complex combination of the rates of the individual steps detailed in scheme 2. The observed initial rate surely reflects the rate of the first initiation step (1) as well as the rates of the rate determining propagation steps (2) and (4). Stabilizing the generated radical DH· will enhance the rate of the above three steps. The formation of $DH^{\cdot}$ from $DH_2$ lowers the electron density on the oxygen atom and that explains the enhanced autoxidation rate with the electron releasing power of the substituent at position 2. The good correlation with $\sigma_p^+$ as reported herein clearly indicates the role of resonance and partial distribution of charge in stabilizing the generated pyrimidine radical.

The compounds of the present invention possess absorption characteristics in the UV region. In particular, the compound of formula (II) exhibited an extraordinary and broad absorption covering wavelengths between 270-410 nm with a $\lambda_{max}$ of 353 nm (**Figure 3**). Absorption properties of compounds of formula (III) are displayed in Table 1.

Consequently, the compounds (I-III) of the present invention may be used as sun protecting agents in an appropriate topical formulation comprising suitable additives known for sun protection lotions. None limiting additives are selected from oils, aqueous additives, surfactants, emulsifiers.

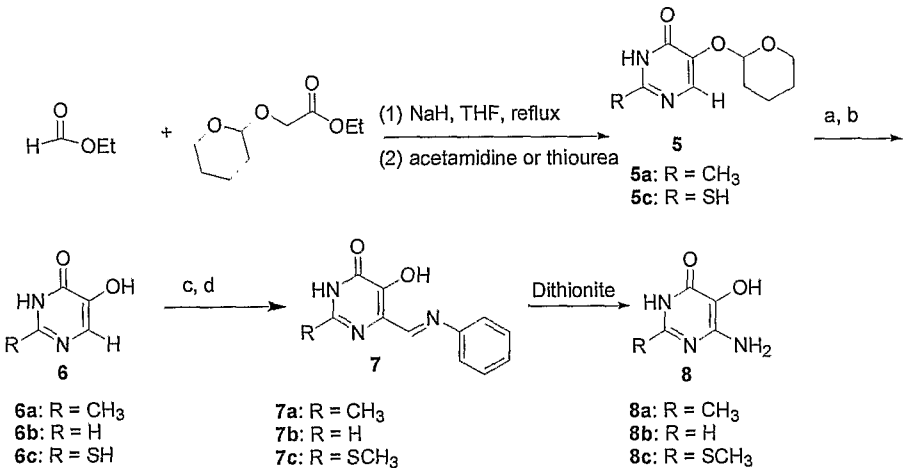
Alternatively, the topical sun protecting formulation of the present invention may further comprise at least one additional organic or inorganic sun protecting agent. Non limiting examples of the at least one additional sun protecting agent are derivatives of anthranilates, benzophenones, camphors, cinnamates, dibenzoylmethanes, p–aminobenzoates, salicylates, zinc oxide, titanium dioxide and mixtures thereof.

The sun screen formulations of the present invention may also be encapsulated in appropriate encapsulating agent thus rendering their environment hydrophobic and aiding in dispersion on the skin.

**Experimental**

The numbering of the compounds whose synthesis is given in examples 1-11 are depicted from the following shortened Scheme 3:

**Scheme 3:**




[a]$H_3O^+$ for **6a**, **6c**. [b]Raney Ni for **6b**. [c] $PhN_2Cl$ for **7a** and **7b**. [d]$(MeO)_2SO_2$ then $PhN_2Cl$ for **7c**.

**Example 1: 2-Methyl-5-(tetrahydro-2*H*-pyran-2-yloxy)pyrimidin-4(3*H*)-one 5a:** To a suspension of sodium hydride (4.60 g in 55-60% paraffin oil), dry ether (50 $cm^3$) and dry ethyl formate (7.84 g) were added. Then (tetrahydropyran-2-yloxy)-acetic acid ethyl ester (20 g) was added dropwise under continuous stirring. After the mixture was refluxed for 2 h, acetamidine (4.3 g) was added. After the removal of ether from the reaction mixture, the remained ethanolic solution was refluxed for 4 h. Then the mixture was cooled and the volatile solvents were removed by rotory- evaporator. The residue was redissolved in water and filtered. The filtrate was acidified by acetic acid in an ice bath and the white precipitate was filtered, washed with water and dried under reduced

pressure at 100 °C. (9.0 g, 58 %); (Found: C 55.25; H 47.54; N 13.19. Calc. for $C_{10}H_{16}N_2O_3$: C 55.59; H 7.60; N 13.20 %). Mp 149-151 °C; $\delta_H$ (300 MHz; $DMSO_d$) 1.23-2.03 (6H, m), 2.27 (3H, s), 3.23-4.04 (2H, m), 5.47 (1H, bs), 7.60 (1H, s), 10.73 (1H, bs). $\nu_{max}$cm$^{-1}$ 1670, 1610, 1385, 1310, 1205, 1190, 1120, 980, 910, 820, 775 and 740; MS(EI): m/z (%) 210 (100, $M^+$, $C_{10}H_{14}N_2O_3$,), 126 ($M^+$, -$C_5H_8O$), 125 ($M^+$-$C_5H_9$).

**Example 2: 5-Hydroxy-2-methylpyrimidin-4(3*H*)-one 6a.**

A few crystals of *p*-toluenesulfonic acid were added to a solution of **1a** (6.57 g) in hot methanol. After cooling the mixture in an ice bath, white crystals were formed. The crystals were filtered and dried under vacuum at 100 °C. (2.5 g, 63 %); Mp > 300 °C; $\delta_H$ (300 MHz; $DMSO_d$) 2.2 (3H, s), 7.27 (1H, s), 9.27 (1H, bs), $\nu_{max}$cm$^{-1}$ 3300, 1670, 1620, 1420, 1380, 1245, 1110, 1020, 875 and 780; MS(EI): m/z (%) 126 (100, $C_5H_6N_2O_2$, $M^+$), 108 ($M^+$, -$H_2O$), 100 ($M^+$, -26).

**Example 3: 5-Hydroxy-2-methyl-6-phenylazo-3*H*-pyrimidin-4-one 7a.**

Diazotation of aniline (1.17 g) was done in hydrochloric acid (3.9 cm$^3$) and water (8 cm$^3$) by addition of sodium nitrite (0.87 g) in water (6 cm$^3$) at 0-5 °C. Then sodium acetate (3.1 g) was added slowly under continuous stirring, followed by the addition of a solution of **6a** (1.59 g) in 10% sodium hydroxide (10.4 cm$^3$). After stirring for 30 min, the reaction mixture was left for overnight at 4 °C. Then the reaction was warmed to 40 °C for 1 h and filtered. The red crystals formed were washed and dried under vacuum at 100 °C. (1.61 g, 56 %); (Found: C 57.60; H 4.22. Calc. for $C_{11}H_{10}N_4O_2$: C 57.89; H 4.35 %); Mp 243-245 °C;$\delta_H$ (300 MHz; $DMSO_d$) 1.95 (3H, s), 6.44-7.73 (5H, m), 11.19 (1H, bs), 11.64 (1H, bs); $\nu_{max}$cm$^{-1}$ 3220, 3180, 1710, 1670, 1600, 1520, 1470, 1430, 1360, 1280, 1250, 1050, 800, 775, 715, 700 and 660; MS(EI): m/z (%) 230 (25, $C_{11}H_{10}N_4O_2$, $M^+$), 105 (100, $C_6H_5N_2^+$).

**Example 4: 6-Amino-5-hydroxy-2-methylpyrimidin-4(3*H*)-one 8a.** A solution of **7a** (1.61 g) in water (15 cm$^3$) was heated to 60-70 °C, an excess of sodium dithionite was added to the solution in batches until a bright yellow color was obtained and the solution was cooled in an ice bath. The white crystals formed were washed with water and dried under vacuum at 100 °C. (0.44 g, 44 %); (Found: C 42.53; H 4.98; N 29.46. Calc. for $C_5H_7N_3O_2$: C 42.55; H 4.96; N 29.79 %); Mp > 300 °C; $\delta_H$ (300 MHz;

$DMSO_d$) 2.13 (3H, s), 5.36 (2H, bs), 7.85 (1H, bs), 11.66 (1H, bs); $\tilde{\nu}_{max}cm^{-1}$ 3420, 3320, 3160, 1600, 1440, 1380, 1280, 1210, 1020, 990, 900, 790 and 770; MS(EI): m/z (%) 141 (100, $C_5H_7N_3O_2$, $M^+$).

**Example 5: 2-Mercapto-5-(tetrahydro-pyran-2-yloxy)-3*H*-pyrimidin-4-one 5c.**

Identical procedure to the synthesis of **5a**, except for the addition of thiourea (15.29 g) instead of acetamidine. White crystals were obtained. (25.0 g, 54.5 %); (Found: C 47.15; H 5.38; S 14.49. Calc. for $C_9H_{12}N_2O_3S$: C 47.37; H 5.26; S 14.00 %); Mp > 300 °C; $\delta_H$ (300 MHz; $DMSO_d$) 0.8-1.97 (6H, m), 3.23-3.80 (2H, m), 5.27 (1H, bs), 7.16 (1H, d, $J_{HNCH}$= 6.0 Hz), 10.8 (1H, bs), 11.3 (1H, bs); $\tilde{\nu}_{max}cm^{-1}$ 3150, 3080, 1630, 1570, 1250, 1200, 1180, 1150, 1110, 1020, 980, 940, 900, 870, 810 and 670; MS(EI): m/z (%) 147 (100, $M^+$-81).

**Example 6: 5-Hydroxy-2-mercapto-3*H*-pyrimidin-4-one 6c.**

A suspension of **5c** (6.0 g) in 1M $H_2SO_4$ (30 $cm^3$) was stirred for 2 h. Then the product was filtered and washed with water, methanol and ether and dried under vacuum at 100 °C. (3.2 g, 84.4 %); (Found: C 33.53; H 2.60; N 19.30; S 22.96. Calc. for $C_4H_4N_2O_2S$: C 33.33; H 2.78; N 19.44; S 22.22 %); Mp > 300 °C;$\delta_H$ (300 MHz; $DMSO_d$) 6.97 (1H, d, $J_{HNCH}$= 6.0 Hz), 9.60 (1H, bs), 10.27 (1H, bs); $\tilde{\nu}_{max}cm^{-1}$ 3240, 3100, 1660, 1580, 1400, 1290, 1230, 1170, 1140, 890, 820, 760, 750 and 690; MS(EI): m/z (%) 144 (100, $C_4H_4N_2O_2S$, $M^+$).

**Example 7: 5-Hydroxy-2-methylsulfanyl-6-phenylazo-3*H*-pyrimidin-4-one 7c.**

**6c** (2.9 g) was dissolved in a solution of sodium hydroxide (1.8 g) in water (12 $cm^3$) and heated to 40 °C. Dimethylsulfate (3.0 g) was added dropwise while vigorously stirring and then the mixture was cooled in an ice bath and filtered. The filtrate was acidified with concentrated hydrochloric acid and was left overnight at 4 °C. The formed crystals were filtered, successively washed with water, methanol and ether and dried under vacuum at 100 °C. The 2-methylthio-4,5-dihydroxypyrimidine formed (1.4 g) was subjected to the same diazotization procedure as **3a**. (1.5 g, 74.0 %); Mp 213-215 °C;$\delta_H$ (300 MHz; $DMSO_d$) 2.73 (3H, s); 6.97-7.83 (5H, m); 10.73 (1H, bs).$\tilde{\nu}_{max}cm^{-1}$ 3480, 3200, 3100, 1710, 1660, 1590, 1510, 1450, 1250, 1150, 1030, 990, 770, 750, 690 and

640; MS(EI): m/z (%) 262 (10, $C_{11}H_{10}N_4O_2S$, $M^+$), 105 (100, $C_6H_5N_2^+$), 91 ($C_6H_5N^+$), 77 ($C_6H_5^+$).

**Example 8: 6-Amino-5-hydroxy-2-(methylthio)pyrimidin-4-(3H)-one 8c.**
Identical to the procedure for the synthesis of **8a**, except for the use of **7c** (1.0 g) instead of **7a**. White crystals were obtained. (0.43 g, 66 %); (Found: C 34.27; H 4.08; N 24.21; S 19.00. Calc. for $C_5H_7N_3O_2S$: C 34.38; H 4.05; N 24.28; S 18.50 %); Mp 243-245 °C; $\delta_H$ (300 MHz; $DMSO_d$) 2.45 (3H, s); 5.87 (2H, bs), 7.90 (1H, bs); $\tilde{\nu}_{max}cm^{-1}$ 3250, 3380, 1640, 1600, 1570, 1410, 1330, 1240, 970, 830 and 760; MS(EI): m/z (%) 173 (100, $C_5H_7N_3O_2S$, $M^+$).

**Example 9: 5-Hydroxypyrimidin-4(3*H*)-one 6b.**
To a solution of water (76 $cm^3$) and concentrated aqueous ammonia (7.6 $cm^3$), **5c** (11.0 g) was added followed by the addition of Raney nickel (40.0 g). The mixture was refluxed for 4 h then it was cooled and filtered. All the volatile solvents were removed by rotor-evaporator and the residue was re-dissolved in methanol. After addition of ether, pink crystals precipitated out of the solution, and were dried under vacuum at 100 °C. (2.5 g, 46 %); Mp 265-267 °C;$\delta_H$ (300 MHz; $DMSO_d$) 7.40 (1H, s), 7.67 (1H, s); $\tilde{\nu}_{max}cm^{-1}$ 1640, 1600, 1360, 1300, 1270, 1100, 930, 880, 790, 780 and 615; MS(EI): m/z (%) 112 (100, $C_4H_4N_2O_2$, $M^+$).

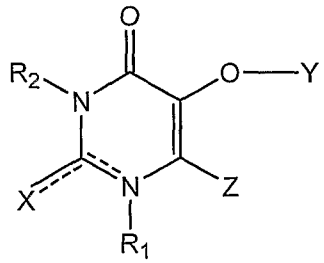
**Example 10: 5-Hydroxy-6-phenylazo-3*H*-pyrimidine-4-one 7b.** Identical to the procedure for the synthesis of **7a** except for the addition of **6b** (1.12 g) instead of **6a.** White crystals were obtained. (1.9 g, 88 %); Mp 244-245 °C; $\delta_H$ (300 MHz; $DMSO_d$) 6.83-7.76 (6H, m), 11.88 (1H, bs); $\tilde{\nu}_{max}cm^{-1}$ 3490, 3290, 1700, 1650, 1615, 1600, 1590, 1500, 1450, 1300, 1240, 1170, 1120, 1015, 900, 875, 750, 730, 680, 660, 640, 660 and 640; MS(EI): m/z (%) 216 (15, $C_{10}H_8N_4O_2$, $M^+$), 105 (100, $C_6H_5N_2^+$), 91 ($C_6H_5N^+$), 77 ($C_6H_5^+$).

**Example 11: 6-Amino-5-hydroxypyrimidin-4(3*H*)-one 8b.** Identical to the procedure for the synthesis of **8a** except for the addition of **7b** (1.0 g) instead of **7a**. (0.45 g, 76 %); (Found: C, 38.02; H, 3.75; N, 33.35. Calc. for $C_4H_5N_3O_2$: C 37.80; H 3.94; N 33.07 %)Mp > 300 °C; $\delta_H$ (300 MHz; $DMSO_d$ ) 5.83 (2H, bs), 7.56 (1H, s), 11.79 (1H, bs);

$\tilde{\nu}_{max}$cm$^{-1}$ 3470, 3140, 1670, 1640, 1620, 1440, 1370, 1250, 1170, 1010, 890, 810, 770 and 650; MS(EI): m/z (%) 127 (100, $C_4H_5N_3O_2$, $M^+$).

**CLAIMS:**

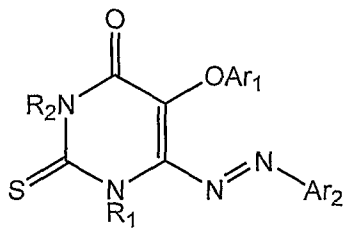
**1.** A pyrimidine derivative of formula (I):



(I)

wherein ------ denotes an optional double bond, where one of the two optional double bonds being a double bond and the other a single bond; $R_1$ is null, hydrogen or $C_{1-6}$alkyl which may be optionally substituted with halogen; $R_2$ is hydrogen or $C_{1-6}$alkyl which may be optionally substituted with halogen; X is hydrogen, $C_{1-4}$alkyl, S-$CH_3$, SH or =S; Y is hydrogen, optionally substituted tetrahydropyran, tetrahydrothiopyran, dithiane, or an optionally substituted aryl or heteroaryl; and Z is (a) $NH_2$; (b) hydrogen (c) -N=NAr, Ar being optionally substituted aryl group.

**2.** A thia-aza- pryrimidine according to claim 1 of formula (II):

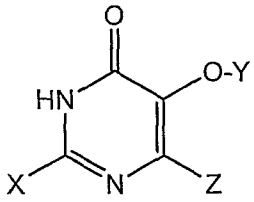


(II)

wherein $R_1$ and $R_2$ are independently selected from hydrogen or $C_{1-6}$alkyl that may be optionally substituted with halogen; $Ar_1$ is selected from the group consisting of optionally substituted tetrahydropyran, tetrahydrothiopyran, dithiane, aryl or heteroaryl; and $Ar_2$ is an optionally substituted aryl group.

**3.** A thia-aza- pryrimidine according to claim 2, wherein $R_1$ and $R_2$ are the same or different and are hydrogen or $C_{1-6}$alkyl; and $Ar_1$ and $Ar_2$ may be the same or different and are an aryl group optionally substituted with one or two $C_{1-6}$alkyl groups.

**4.** A pyrimidine according to claim 1 of formula (III):



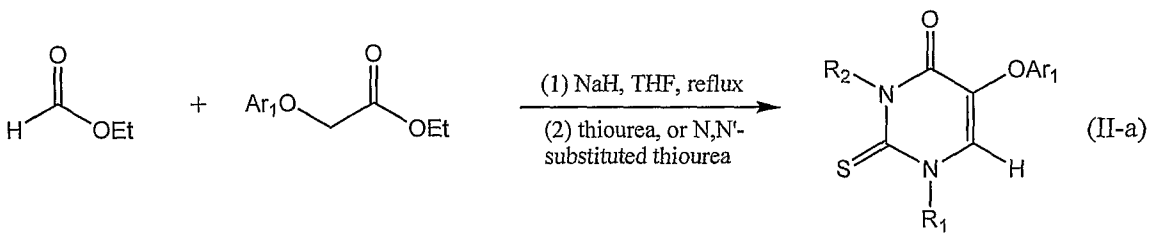
(III)

wherein X is hydrogen, $C_{1-4}$alkyl, S-$CH_3$, SH; Z is (a) $NH_2$; (b) hydrogen (c) -N=NAr, Ar being an optionally substituted aryl group; Y is hydrogen, optionally substituted tetrahydropyran or aryl.

**5.** A pyrimidine according to claim 4 wherein X is hydrogen, methyl, ethyl or propyl, SH or S-$CH_3$; Y is hydrogen; and Z is $NH_2$.

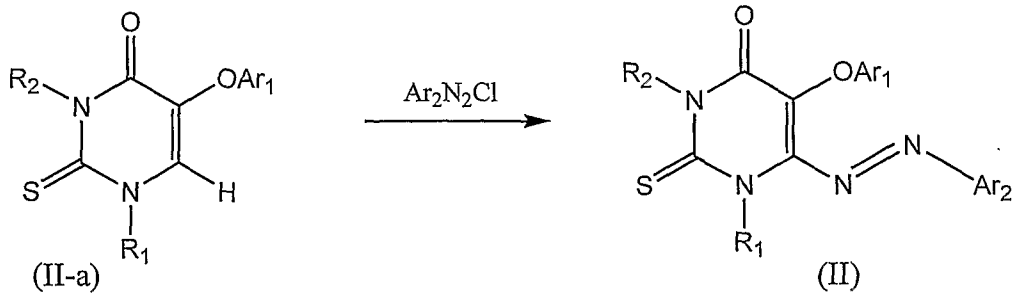
**6.** A process for the manufacture of a thia-aza-pyrimidine of formula (II) as defined in Claim 2, comprising:

(a) reacting formic ethyl formate with α-aryloxy-acetic acid ethylester in the presence of a base and thiourea or N,N'-substituted thiourea to yield an optionally substituted thia-pyrimidine of formula (II-a), according to the following reaction scheme:




(II-a)

(b) reacting the optionally substituted thia-pyrimidine of formula (II-a) with aryldiazonium chloride, the aryl group being optionally substituted, to yield the thia-aza-pyrimidine of formula (II), according to the following reaction scheme:

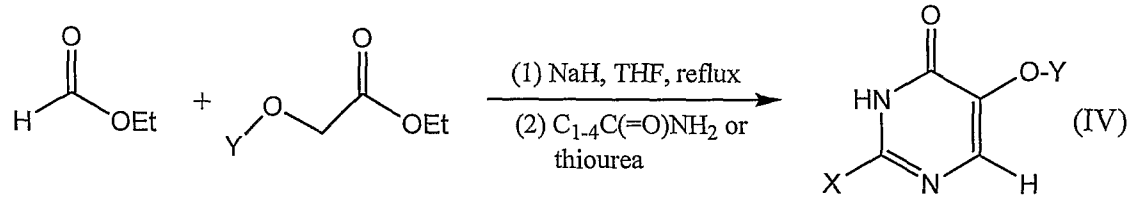



(II-a) (II)

wherein $R_1$, $R_2$, $Ar_1$ and $Ar_2$ are as defined in Claim 2.

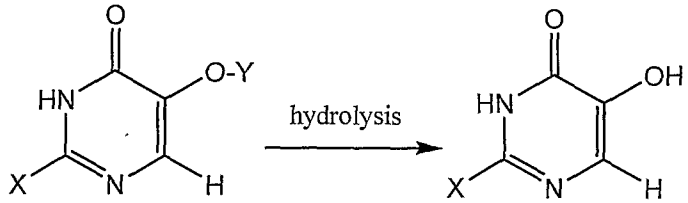
**7.** A process for the manufacture of a pyrimidine of formula (III-a), comprising:

(a) reacting ethyl formate and the ethylester of the appropriate α-oxy acetic acid derivative in the presence of sodium hydride and $C_{1-4}C(=O)NH_2$ or thiourea to yield a compound of formula (IV), according to the following reaction scheme:



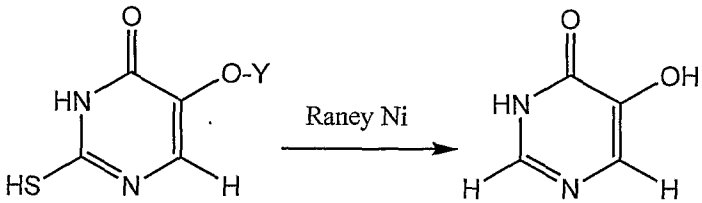

wherein X is $CH_3$ or SH and Y hydrogen, tetrahydropyran or aryl;

(b) hydrolyzing a compound of formula (IV) to yield a compound of formula (III-a), according to the following reaction scheme:



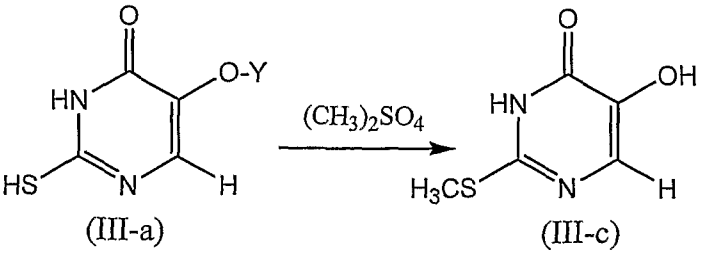

wherein X is $C_{1-4}$ or SH.

**8.** A process for the manufacture of a pyrimidine of formula (III-b), comprising: reacting a compound of formula III-a of claim 7, wherein X is SH with Raney Ni to yield a compound of formula (III-b) according to the following reaction scheme:

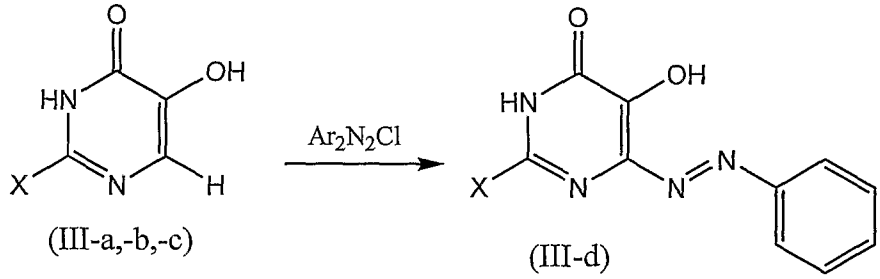



**9.** A process for the manufacture of a compound of formula (III-c) wherein X is $SCH_3$, Y and Z are hydrogen, comprising:

reacting a compound of formula (III-a) of claim 7 wherein X is SH with $(CH_3)_2SO_4$ to yield a compound of formula (III-c) according to the following reaction scheme:

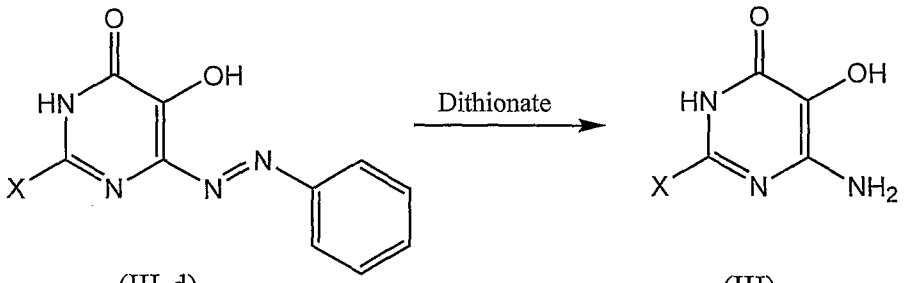


**10.** A process for the manufacture of a compound of formula (III-d) wherein X is hydrogen, SH, $SCH_3$ or $C_{1-4}$, Y is H and Z is $-N=NAr_2$ comprising:
reacting any one of compounds of formulae (III-a), (III-b), (III-c) as defined in any one of claims 7-9 with a diazotizing reagent of formula $-N=NAr_2$, $Ar_2$ as defined in claim 4; according to the following reaction scheme:




(III-a,-b,-c) (III-d)

**11.** A process for the manufacture of a compound of formula III, wherein X is hydrogen, SH, $SCH_3$ or $C_{1-4}$, Y is hydrogen and Z is $NH_2$, comprising reacting a compound of formula III-d with dithionate according to the following reaction scheme:




(III-d) (III)

**12.** A compound of formulae III-a, III-b, III-c or III-d.

**13.** A compound of formula III wherein X is hydrogen, SH, $SCH_3$ or $C_{1-4}$, Y is hydrogen and Z is $NH_2$.

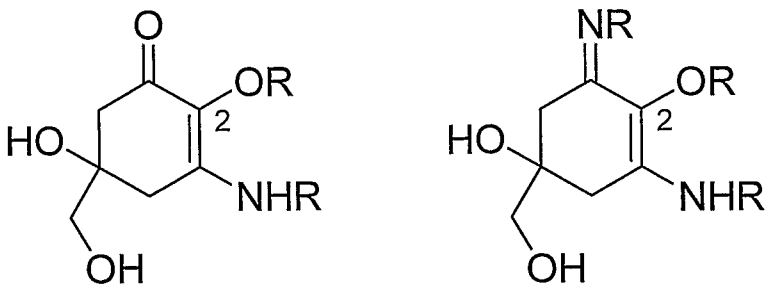
**14.** A topical formulation for providing protection from ultra violet irradiation comprising an effective amount of a compound of formula (I) of claim 1 together with suitable additive or excipient.

**15.** A topical formulation for providing protection from ultra violet irradiation comprising an effective amount of a compound of formula (II) of claim 2 together with suitable additive or excipient.

**16.** A topical formulation for providing protection from ultra violet irradiation comprising an effective amount of a compound of formula (III) of claim 4 together with suitable additive or excipient.

17. A topical formulation according to any one of claims 14-16 further comprising an additional sun-protecting agent.

18. A topical formulation according to claim 17, wherein said additional sun-protecting agent is chosen from the group comprising of derivatives of anthranilates, benzophenones, camphors, cinnamates, dibenzoylmethanes, p–aminobenzoates, salicylates, zinc oxide, titanium dioxide or mixtures thereof.




**1** **2**

Figure 1

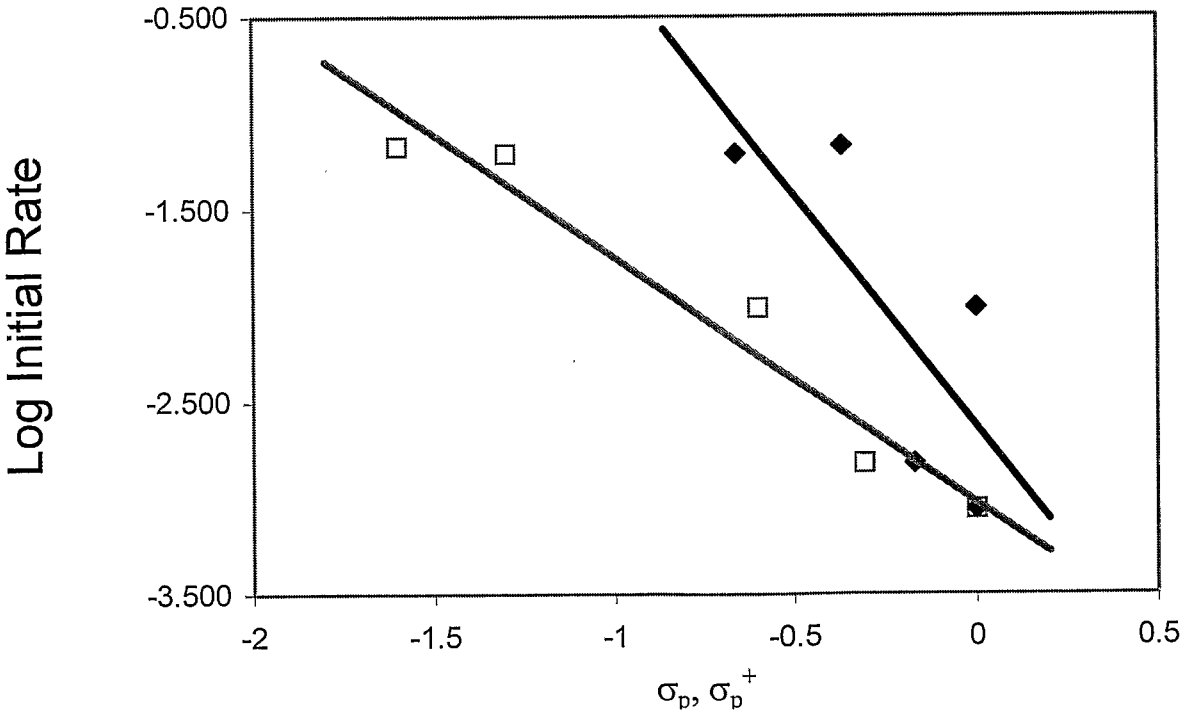
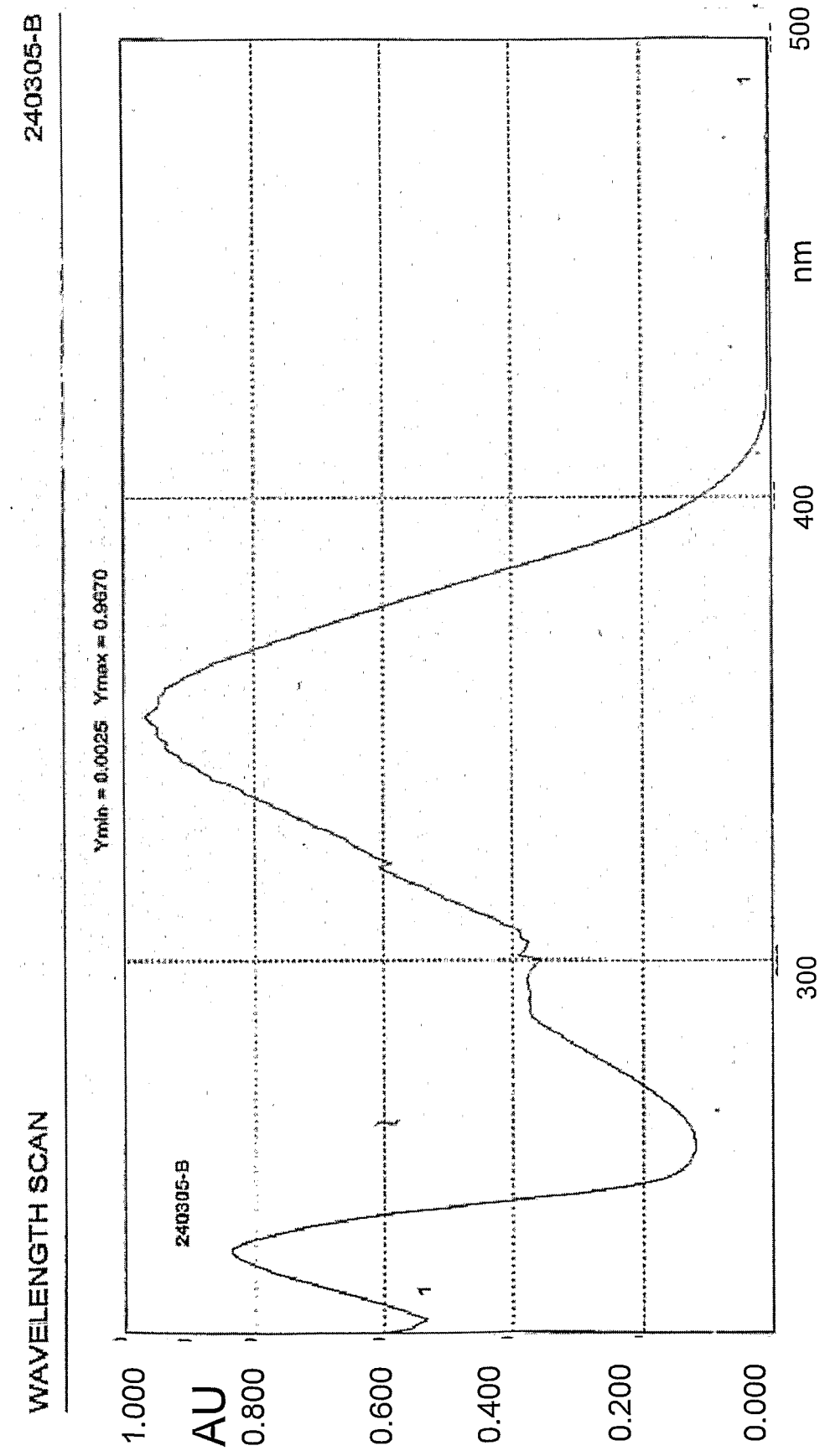



Figure 2


WAVELENGTH SCAN
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240305-B
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1
AU
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0.800
0.600
0.400
0.200
0.000
300
400
500
nm

Figure 3

# INTERNATIONAL SEARCH REPORT

International application No
PCT/IL2007/000471

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D239/54 C07D239/60 A61K8/49

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
C07D A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data, BEILSTEIN Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

| Category* | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|---|---|---|
| X | D. T. HURST: "The Synthesis and Some Reactions of Chloropyrimidines." HETEROCYCLES, vol. 22, no. 1, 1984, pages 79-84, XP009088309 page 80, compound 1(a) ----- | 1,4,5,13 |
| X | J. KOSARY ET.AL.: "VARHATOAN KARDIOTONIAS HATASU PIPRIMIDIN-SZARMAZEKOK ELöALLITASA" ACTA CHIMICA HUNGARICA, vol. 59, no. 6, 1989, pages 241-247, XP002119936 page 244, compound 13c ----- -/-- | 1,4,5,13 |

[X] Further documents are listed in the continuation of Box C.

[X] See patent family annex.

* Special categories of cited documents :

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"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

| Date of the actual completion of the international search | Date of mailing of the international search report |
|---|---|
| 21 August 2007 | 30/08/2007 |

| Name and mailing address of the ISA/ | Authorized officer |
|---|---|
| European Patent Office, P.B. 5818 Patentlaan 2<br>NL - 2280 HV Rijswijk<br>Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,<br>Fax: (+31-70) 340-3016 | Helps, Ian |

# INTERNATIONAL SEARCH REPORT

International application No
PCT/IL2007/000471

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

| Category* | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|---|---|---|
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