



INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification ⁵ : C07D 487/04, A61K 31/41, C07D 403/14, A61K 31/44, C07D 405/14	A1	(11) International Publication Number: WO 94/17068 (43) International Publication Date: 4 August 1994 (04.08.94)
(21) International Application Number: PCT/IB94/00010 (22) International Filing Date: 18 January 1994 (18.01.94) (30) Priority Data: 9300127-9 19 January 1993 (19.01.93) SE (71) Applicant (for all designated States except US): BRITISH TECHNOLOGY GROUP LIMITED [GB/GB]; 101 Newington Causeway, London SE1 6BU (GB). (72) Inventors; and (75) Inventors/Applicants (for US only): ALBRECHTSEN, Sten [DK/DK]; Aalholmparken vej 8 no. 9, DK-3400 Hilleroed (DK). HANSEN, Jens [DK/DK]; Petuniavej 3, DK-3450 Alleroed (DK). LANGVAD, Eyvind [DK/DK]; Skodsborgparken 20, DK-2942 Skodsborg (DK). ERIKSOO, Edgar [SE/SE]; Skaanegatan 22A, S-252 52 Helsingborg (SE). JOHANSSON, Kaj [SE/SE]; Rektorsgatan 22, S-254 36 Helsingborg (SE). LUNDVALL, Karl-Erik [SE/SE]; Espehogsgatan 69, S-262 53 Angelholm (SE). (74) Agent: STEPHENSON, Gerald, Frederick; Patents Dept., British Technology Group Limited, 101 Newington Causeway, London SE1 6BU (GB).		(81) Designated States: AU, CA, JP, KR, NZ, US, European patent (AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE). Published <i>With international search report.</i>
(54) Title: TRICYCLIC 1,2,4-TRIAZOLO COMPOUNDS WITH ANTI-INFLAMMATORY AND IMMUNOMODULATORY PROPERTIES (57) Abstract A compound of general formula (I), wherein A is 1,2-phenylene, optionally mono- or di-substituted by an alkyl group of 1-4 carbon atoms, an alkoxy group of 1-4 carbon atoms, CF₃, halogen, OH or NR₂R₃ wherein R₂ and R₃ which may be the same or different are H or an alkyl group of 1-4 carbon atoms; 4-cyclohexen-cis-1,2-ylene; 1-cyclohexen-1,2-ylene; cis-1,2-cyclohexylene; and R₁ is a 5 or 6-membered heterocyclic ring containing one or two of the heteroatoms N, O and S, optionally mono- or di-substituted by an alkyl group of 1-4 carbon atoms an alkoxy group of 1-4 carbon atoms, halogen, or OH; a cyclohexyl group; a group of formula (II), wherein R₅, R₆ and R₇ which may be the same or different are H, OH, an alkyl group of 1-4 carbon atoms, an alkoxy group of 1-4 carbon atoms, CF₃, halogen or the group NR₂R₃ wherein R₂ and R₃ are as defined above, the compound optionally being in the form of a pharmaceutically acceptable pro-drug formed at one or more hydroxy groups in a substituted 1,2-phenylene group A and/or a substituted group R₁ for use in therapy. (I) (II)		

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AT	Austria	GB	United Kingdom	MR	Mauritania
AU	Australia	GE	Georgia	MW	Malawi
BB	Barbados	GN	Guinea	NE	Niger
BE	Belgium	GR	Greece	NL	Netherlands
BF	Burkina Faso	HU	Hungary	NO	Norway
BG	Bulgaria	IE	Ireland	NZ	New Zealand
BJ	Benin	IT	Italy	PL	Poland
BR	Brazil	JP	Japan	PT	Portugal
BY	Belarus	KE	Kenya	RO	Romania
CA	Canada	KG	Kyrgyzstan	RU	Russian Federation
CF	Central African Republic	KP	Democratic People's Republic of Korea	SD	Sudan
CG	Congo	KR	Republic of Korea	SE	Sweden
CH	Switzerland	KZ	Kazakhstan	SI	Slovenia
CI	Côte d'Ivoire	LI	Liechtenstein	SK	Slovakia
CM	Cameroon	LK	Sri Lanka	SN	Senegal
CN	China	LU	Luxembourg	TD	Chad
CS	Czechoslovakia	LV	Latvia	TG	Togo
CZ	Czech Republic	MC	Monaco	TJ	Tajikistan
DE	Germany	MD	Republic of Moldova	TT	Trinidad and Tobago
DK	Denmark	MG	Madagascar	UA	Ukraine
ES	Spain	ML	Mali	US	United States of America
FI	Finland	MN	Mongolia	UZ	Uzbekistan
FR	France			VN	Viet Nam
GA	Gabon				

TRICYCLIC 1,2,4-TRIAZOLO COMPOUNDS WITH ANTI-INFLAMMATORY AND IMMUNOMODULATORY PROPERTIES

Field of the Invention

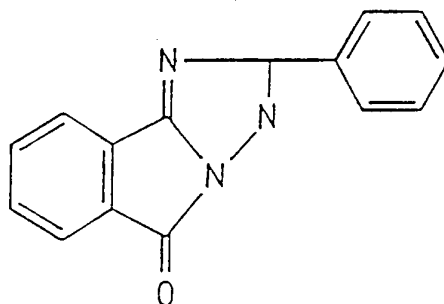
This invention relates to tricyclic condensed 1,2,4-triazolo derivatives. These compounds are useful in therapy.

5 Background of the InventionDescription of the Prior Art

A group of triazoloisoindole derivatives have been described by Gruppo Lepetit S.p.A. (Triazoloisoindole derivatives. Ger. 10 offen 2,424,670) and were shown to have postcoital contraceptive activity. These compounds were reported to have anti-inflammatory activity in the carrageenin oedema test in rats.

The compound 2-phenyl-5H-1,2,4-triazolo[5,1-a]isoindol-5-one, the structural formula of which is shown below

15



20

has been described in the literature. Korshak et al. (Izv. Akad. Nauk Gruz. SSR Ser. Khim 1976, 2 103-108) described the synthesis 25 of this compound from phthalic anhydride and benzamidrazone. Korhsak et al (Macromolecules 1975, 582-593) discloses this compound as an intermediate in the production of polymeric materials. The thermal and hydrolytic stability of this compound was reported by Korshak et al (Izv. Akad. Nauk SSR, Ser. Khim 30 1977, 1381-1388) and thermal degradation experiments and cleavage by nucleophilic agents have been described by Korshak et al (Izv. Akad. Nauk SSR, Ser. Khim 1976, 313-320 and Izv Akad. Nauk SSR, Ser. Khim 1976, 376-379).

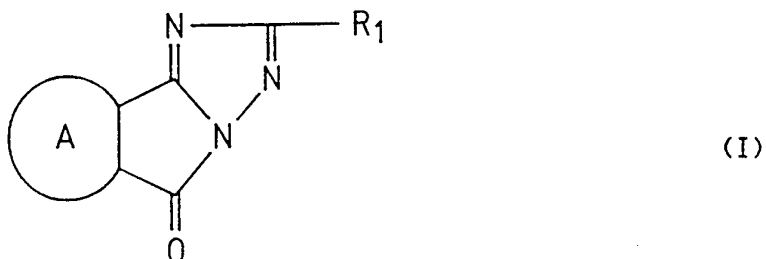
- 2 -

This compound has not however been shown to possess any useful therapeutic properties. Additionally, even though a considerable amount of time has elapsed since the first synthesis of this compound, no derivatives of this compound have been synthesised.

It has surprisingly been found that the compound 2-phenyl-5H-1,2,4-triazolo[5,1-a]isoindol-5-one and substituted derivatives of this compound possess anti-inflammatory and immunomodulatory properties and thus are useful in therapy, especially in the treatment of autoimmune disorders such as chronic inflammatory diseases including psoriasis, rheumatoid arthritis and inflammatory bowel disease.

Description of the Invention

Accordingly, the invention provides a compound of the general formula (I) below:



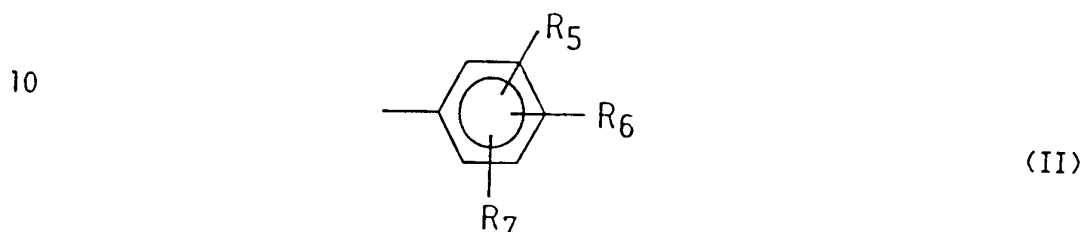
wherein A is

- 1,2-phenylene, optionally mono- or di-substituted by an alkyl group of 1-4 carbon atoms, an alkoxy group of 1-4 carbon atoms, CF₃, halogen, OH or NR₂R₃ wherein R₂ and R₃ which may be the same or different are H or an alkyl group of 1-4 carbon atoms,
- 4-cyclohexen-cis-1,2-ylene
- 1-cyclohexen-1,2-ylene
- cis-1,2-cyclohexylene

- 3 -

and R_1 is

- a 5 or 6 membered heterocyclic ring containing one or two of the heteroatoms N, O and S, optionally mono- or di-substituted by an alkyl group of 1-4 carbon atoms, an alkoxy group of 1-4 carbon atoms, halogen, or OH
- a cyclohexyl group
- a group of formula (II) below



- 15 wherein R_5 , R_6 and R_7 which may be the same or different are H, OH, an alkyl group of 1-4 carbon atoms, an alkoxy group of 1-4 carbon atoms, CF_3 , a halogen or the group NR_2R_3 wherein R_2 and R_3 are as defined above,
- 20 the compound optionally being in the form of a pharmaceutically acceptable pro-drug formed at one or more hydroxy groups in a substituted 1,2-phenylene group A and/or a substituted group R_1 for use in therapy.

Description of the preferred embodiments

- The preferred compounds are those in which A is
- 25 1,2-phenylene, optionally mono- or di- substituted with substituents as defined above and R_1 is a phenyl group, a pyridyl, thienyl, pyrazinyl or furyl group, optionally mono- or di- substituted with substituents as defined above. When A and R_1 are substituted by halogens, then preferably the halogens are
- 30 F or Cl.

The most preferred compound is 2-phenyl-5H-1,2,4-triazolo [5,1-a]isoindol-5-one.

- It will be appreciated that with the exception of the compound 2-phenyl-5H-1,2,4-triazolo[1,1-a]isoindol-5-one (A is
- 35 1,2-phenylene and R_1 is phenyl in the above formula (I)), the

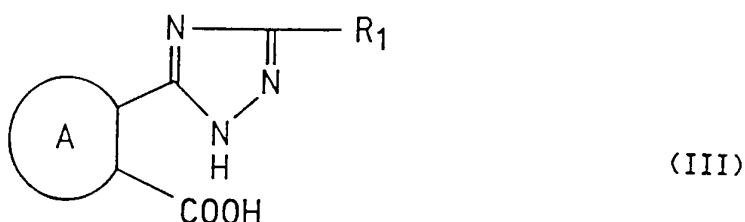
- 4 -

compounds of formula (I) above are novel per se.

Accordingly the invention further provides a compound of the general formula (I) defined above but with the proviso that when A is 1,2-phenylene, R₁ is not phenyl.

5 The compound of the general formula (I) may be prepared by for example the following methods. One method for the preparation of the compounds of the general formula (I) is the cyclization of the open-chain carboxylic of general formula (III) below

10



15

by using conventional methods for the preparation of carboxamides from carboxylic acids and amines.

20 One such method is to treat a carboxylic acid of the general formula (III) with a dehydrating agent such as dicyclohexylcarbodiimide. Another such method is to convert the carboxylic acid group of the compounds (III) into a reactive derivative such as an acid chloride or an anhydride which by ring closure forms the desired compound of the general formula (I).

25 Other reagents useful for the cyclization of compound, of the general formula (III) are 1,1-carbonyl-diimidazole and the open chain sulfonyl halides such as p-toluenesulfonylchloride and methanesulfonylchloride.

30 The intermediate carboxylic acids (III) are known compounds and can be prepared by conventional methods (J.B. Polya. "1,2,4,-triazoles" in A.R. Katritzky, Ch. W. Rees (Editors) Comprehensive Heterocyclic Chemistry 5, 1984. Pergamon Press Oxford).

- 5 -

A compound of the invention may be administered to a subject (including a human) in the form of a pharmaceutical composition. Accordingly the invention further provides a pharmaceutical composition comprising a compound of formula (I) in association
5 with a pharmaceutically acceptable diluent or carrier. The pharmaceutical composition may be formulated into various forms for administration purposes. These pharmaceutical compositions are desirably in unitary dosage form adapted for administration orally, rectally, percutaneously, or by parental injection. For
10 example, in preparing the compositions in oral dosage form, any of the usual pharmaceutical media may be employed, such as, for example, water, glycols, oils, alcohols and the like in the case of oral liquid preparations such as suspensions, syrups, elixirs and solutions; or solid carriers such as starches, sugars,
15 kaolin, lubricants, binders, disintegrating agents and the like in the case of powders, pills, capsules and tablets. Because of their ease in administration, tablets and capsules represent the most advantageous oral dosage unit form, in which case solid pharmaceutical carriers are obviously employed. Injectable
20 suspensions may also be prepared in which case appropriate liquid carriers, suspending agents and the like may be employed. In the compositions suitable for percutaneous administration, the carrier optionally comprises a penetration enhancing agent and/or a suitable wettable agent, optionally combined with suitable
25 additives of any nature in minor proportions, which additives do not cause any significant deleterious effects on the skin. Said additives may facilitate the administration on the skin. Said additives may facilitate the administration to the skin and/or may be helpful for preparing the desired compositions. These
30 compositions may be administered in various ways, e.g. as a transdermal patch, as a spot-on or as an ointment. It is especially advantageous to formulate the aforementioned pharmaceutical compositions in dosage unit form for ease of administration and uniformity of dosage. Dosage unit form as

- 6 -

used in the specification and as unitary dosages, each unit containing a predetermined quantity of active ingredient calculated to produce the desired therapeutic effect in association with the required pharmaceutical carrier. Examples
5 of such dosage unit forms are tablets (including scored or coated tablets), capsules, pills, injectable suspensions and the like.

The compounds of formula (I) may also be prepared in the form of pro-drugs in which when A is an OH-substituted 1,2-phenylene group and/or R₁ is an OH-substituted heterocyclic
10 ring or an OH-substituted group of formula (II), the H atom is replaced by a group R₄ wherein R₄ is a pro-drug providing radical.

Pro-drugs of the compounds of the invention may take various forms known as useful in pharmaceutically active compounds. Thus, for example they may be esters, carbonate esters and
15 phosphate esters. Examples of such pro-drug types can be found in P. Krogsgaard-Larson, H. Bundgaard "A textbook of Drug Design and Development" (1991) Harwood Academic Publishers.

In view of the immunomodulatory and anti-inflammatory properties of the compounds of formula (I) it is evident that the
20 present invention is especially useful in the treatment of patients suffering from chronic inflammatory diseases.

Accordingly, the present invention also includes a method for treating chronic inflammatory disease in a subject in need of such treatment which comprises administering to said subject a
25 therapeutically effective amount of a compound of formula (I) as defined hereinbefore. The invention also provides the use of a compound of formula (I) for the manufacture of a novel medicament for use in the treatment of chronic inflammatory diseases.

There are a number of chronic inflammatory diseases such as
30 psoriasis, rheumatoid arthritis and inflammatory bowel disease.

A suitable dosage of the compounds of formula (I) would depend on the severity of the disease being treated. In general it is contemplated that an effective amount would be from 0.01mg/kg to 20mg/kg body weight, more preferably from 0.04mg/kg
35 to 10mg/kg body weight.

- 7 -

The following examples are intended to illustrate and not to limit the scope of the present invention. Unless otherwise stated all parts therein are by weight.

5 Example 1 - Synthesis of 2-phenyl-5H-1,2,4-triazolo[5,1-a]isoindol-5-one

 A mixture consisting of one part of 3-(2-carboxyphenyl)-5-phenyl-H-1,2,4-triazole, 0.82 parts of dicyclohexyl carbodiimide and 10 parts of dimethylformamide was heated at 90°C
10 for one hour. The reaction mixture was then cooled to room temperature and filtered. Twenty parts of water were added to the filtrate and the mixture so obtained was extracted with methylene chloride. The extract was evaporated to dryness in vacuo and the residue was crystallized from ethylacetate to give
15 2-phenyl-5H-1,2,4-triazolo[5,1-a]isoindol-5-one, m.p. 175°C.

 In essentially the same manner the following compounds were obtained from the corresponding starting materials:

20 2-(4-methoxyphenyl)-5H-1,2,4-triazolo[5,1-a]isoindol-5-one,
 m.p. 200°C

 2-(3-methoxyphenyl)-5H-1,2,4-triazolo[5,1-a]isoindol-5-one,
 m.p. >250°C

25 2-(4-chlorophenyl)-5H-1,2,4-triazolo[5,1-a]isoindol-5-one,
 m.p. 275°C

 2-phenyl-8-methoxy-5H-1,2,4-triazolo[5,1-a]isoindol-5-one,

30 2-phenyl-9-fluoro-5H-1,2,4-triazolo[5,1-a]isoindol-5-one,

 2-(4-hydroxyphenyl)-7-chloro-5H-1,2,4-triazolo[5,1-a]isoindol-5-one,

- 8 -

2-(4-fluorophenyl)-5H-1,2,4-triazolo[5,1-a]isoindol-5-one,
m.p.238°C

2-(3,4-dimethoxyphenyl)-5H-1,2,4-triazolo[5,1-a]isoindol-5-one,
5 m.p.237°C

2-phenyl-8-trifluoromethyl-5H-1,2,4-triazolo[5,1-a]isoindol-5-one,

2-phenyl-7-dimethylamino-5H-1,2,4-triazolo[5,1-a]isoindol-5-one,
10

2-(3-trifluoromethylphenyl)-5H-1,2,4-triazolo[5,1-a]isoindol-5-one,
m.p.185°C

Example 2 - Synthesis of 2-(2-pyridyl)-5H-1,2,4-triazolo[5,1-a]
15 isoindol-5-one

Twelve parts of phthalic anhydride were added to a solution of 11 parts of 2-pyridyl-amidrazone in 50 parts of dimethyl sulfoxide and the reaction mixture was stirred at 70°C for three hours.

20 The reaction mixture was then poured into water and the precipitate formed was filtered off and dried.

The dried precipitate was dissolved in 100 parts of N,N-dimethylformamide and 14 parts of 1,1'-carbonyl-diimidazole were added. The reaction mixture was stirred at 80°C for three
25 hours. After cooling, a precipitate formed which was filtered off and dried, to give 2-(2-pyridyl)-5H-1,2,4-triazolo[5,1-a]isoindol-5-one, m.p. >250°C.

In essentially the same manner the following compounds were obtained from the corresponding starting materials:

30

2-(2-thienyl)-5H-1,2,4-triazolo[5,1-a]isoindol-5-one,

2-pyrazinyl-5H-1,2,4-triazolo[5,1-a]isoindol-5-one,

- 9 -

2-(2-furyl)-5H-1,2,4-triazolo[5,1-a]isoindol-5-one,

2-phenyl-5H-5a,6,7,8,9a-tetra-hydro-1,2,4-triazolo[5,1-a]isoindol-5-one,

5

2-phenyl-5H-6,7,8,9-tetra-hydro-1,2,4-triazolo[5,1-a]isoindol-5-one,

10 2-phenyl-5H-5a,6,7,8,9,9a-hexahydro-1,2,4-triazolo[5,1-a]isoindol-5-one,

2-cyclohexyl-5H-1,2,4-triazolo[5,1-a]isoindol-5-one,

15 2-(4-methylphenyl)-5H-1,2,4-triazolo[5,1-a]isoindol-5-one,

2-(4-isobutylphenyl)-5H-1,2,4-triazolo[5,1-a]isoindol-5-one,

Example 3: Manufacturing process for tablets a 20mg

Model batch of 1,000 tablets

20	I	Active Compound, mesh ⁺ 70	20g
		Lactosum, Ph. Nord.	210g
	II	Amylum maidis, Ph. Nord.	75g
		Kollidon 25, BASF	3,5g
25	III	Aqua purificata	q.s.
		Talcum, Ph. Nord.	15g
		Magnesii stearas, Ph. Nord.	<u>1,5g</u>
		Weight of 1,000 tablets	325g

(⁺) The mesh standard is according to the international system of code DIN 4189/1968.

30 Punch: 10,5mm round, flat, scored, bevel-edged.

Mix the screened substances I thoroughly and then moisten with II, whereupon the mixture is granulated through a stainless sieve No. 10 (mesh 25). Dry the granulate in an oven at a maximum temperature of 40°C, then repeat sieving through sieve

- 10 -

No. 10. Add the substances under III and mix thoroughly. Punch tablets with a gross weight of about 325 mg.

Example 4: Preparation of a Suspension for Injection 20 mg/ml

5	Active compound, mesh 100	20mg
	Sodium chloride	8mg
	Carboxy methylcellulose	1mg
	Benzyl alcohol	1mg
	Distilled water to make	1mg

10

Example 5: Preparation of Capsules at 10mg

Active compound	10mg
Magnesium stearate	2mg
Talcum	188mg

15 The substances are mixed and filled in capsules.

Example 6: Preparation of a Cream

A cream containing active compound is produced in the following way:

20 Four grams of active compound are dissolved in mixture of 380g of Macrogol 3000 and 555g Macrogol 400 and 61g of distilled water are added. The mixture so obtained is homogenized to a cream.

25 **Example 7: Anti-inflammatory effects of Compounds of Formula (I): Sensitization Model**

The effects of the compounds of the general formula (I) were determined using the following sensitization model.

30 Male CF/1 mice weighing approximately 25g at the start of the experiment were used. On day 1 the abdomen of the mice was shaved. On day 1 and 2 the mice were sensitized by applying 25 μ l of a 0.5% solution of the allergenic compound 2,4-dinitro-fluorobenzene (DNFB) in a 4:1 acetone: olive oil mixture on the shaved area.

- 11 -

The challenge response was produced on day 7 applying 10 μ l of the DNFB solution used above on the left ear.

The thickness of the ears was measured immediately before and 24 hours after the challenge. The mice were anaesthetised in ether prior to taking the readings.

The test compounds were suspended in a methocel solution. The methocel solution was prepared by dissolving 30g of methocel 4000-HG, 45g of sodium chloride and 25g of Kremofor EL in 5 litres of water and the obtained solution was sterilized. The methocel solutions including the test compounds were administered by intraperitoneal injections 26 and 2 hours before and 22 hours after the challenge. The control group was treated with the methocel solution.

The thickness of the ears is an expression of the inflammatory response. The inhibitory effect of the test compounds is expressed in per cent after comparison with the control groups.

A dose of 400 μ moles per kg of body weight of the compound 2-phenyl-5H-1,2,4-triazolo[5,1-a]isoindol-5-one inhibited the increase in ear thickness by 65.0%. Similar results were obtained with other compounds of the general formula (I).

These results were obtained using the CF/1 outbred strain. The use of outbred strains may give larger biological variabilities when compared to the use of inbred strains. Thus, this test has also been carried out on the Balb/C strain. Investigations have shown that these mice responded similarly to CF/1 mice for DNFB sensitization and challenge. The experimental procedures were the same. The Balb/C mice did not however tolerate being anaesthetised with ether, thus Propanediol (600mg per kg of body weight) was used instead.

- 12 -

**Example 8: Anti-inflammatory effects of compounds of formula (I):
Croton oil induced inflammation**

The effects of the compounds of the general formula (I) were determined using the croton oil induced inflammation of the mouse ear.

Groups consisting of 10 male CF/1 mice weighing approximately 25g at the start of the experiment were used.

The test compounds were administered suspended in a methocel solution (see Example 7). The animals in the control group were treated with the methocel solution.

Two hours after the administration of the test compounds, 10 μ l of a solution of croton oil in acetone (20mg/ml) were applied on the innerside of one of the earlobes of each mouse.

The thickness of the ears was measured immediately before and three hours after the application of the croton oil solution.

The thickness of the ears is an expression of the inflammatory response to croton oil. The inhibitory effect of the test compounds is expressed in per cent after comparison with the control group.

A dose of 400 μ moles per kg of body weight of the compound 2-phenyl-5H-1,2,4-triazolo[5,1-a]isoindol-5-one inhibited the increase in ear thickness by 63.1%. Similar results were obtained with other compounds of the general formula (I).

**Example 9: Anti-inflammatory effects of compounds of formula (I):
Collagen-II arthritis model**

The effects of the compounds of the general formula (I) were determined using the collagen-II arthritis model. In this model, arthritis was induced by chicken-collagen-II immunisation.

Male DBA/1 mice older than 7 weeks at the start of the experiment were immunized using a chicken collagen-II (cc-II) solution (1mg cc-II/ml 0.1M acetic acid) emulsified in complete Freund's Adjuvant (CFA) in the ratio 1:1.

- 13 -

Each mouse was given 200 μ l (100 μ cc-II) of this emulsion subcutaneously in the tail base.

One week later the mice were boosted in a similar way using 100 μ l of the emulsion (50 μ cc-II).

5 The compound 2-phenyl-5H-1,2,4-triazolo[5,1-a]isoindol-5-one was suspended in a methocel solution (See Example 7). The methocel solution including the test compound was administered daily by intraperitoneal injections.

10 Treatments were given on weekdays in the period from day 21 after immunization to day 54.

 The lesions of the four paws were scored by a graded scale from 1-4 (1 = one arthritic joint; 2 = two arthritic joints; 3 = three or more arthritic joints and/or moderate erythema and edema of the paw; 4 = as in 3, but with intense erythema and oedema).
15 The maximum score obtainable for the mouse was thus 4 x 4 = 16 points.

 It was seen that with a dose of 100 μ moles per kg of body weight of the test compound, the development of arthritis was totally eliminated with both the score and the incidence being
20 zero. After 53 days the drug treatment was stopped. Further measurements showed that the arthritis was not eliminated but only suppressed in its development.

 With doses up to 200 μ moles per kg of body weight on weekdays as described above other compounds of the general formula (I)
25 significantly reduced the arthritic response.

**Example 10: Anti-inflammatory effects of compounds of formula (I):
Croton oil induced chronic inflammation**

30 The effects of the compounds of the general formula (I) were determined using the croton oil, induced chronic inflammation of the mouse ear. The thickness of the ears together with the infiltration of neutrophilic granulocytes is an expression of the inflammatory response.

- 14 -

Groups consisting of 10 male CF/1 mice weighing approximately 25g at the start of the experiment were used.

10µl of croton oil in acetone (2mg/ml) was applied daily on the inner side of the ear-lobe on the days 0,2,3,4 and 5.

5 The test compounds were administered suspended in a methocel solution (see Example 7). The animals in the control group were treated with the methocel solution.

The test compounds were administered by intra peritoneal injections on day 2 through 5.

10 The response was measured as the thickness of the ears 24 hours after the latest croton oil and drug treatment. The thickness was measured immediately before the first croton oil application and on day 2 through 6.

15 In addition to the ear thickness the infiltration of neutrophilic granulocytes was semi-quantitated by measuring the myeloperoxidase activity in earpunches taken on day 6.

20 A dose dependent reduction in the induced ear thickness was measured. A dose of 400 µmole per kg body weight of the compound 2-phenyl-5H-1,2,4-triazolo[5,1-a]isoindol-5-one inhibited the increase in ear thickness by 56% when measured on day 6 (IC₅₀=app.300 µmoles per kg of body weight per day).

The neutrophilic granulocyte infiltration was similarly dose dependently reduced with an IC₅₀=app.100 µmoles per kg of body weight per day).

25 Similar results were obtained with other compounds of the general formula (I).

Example 11: Carrageenin induced rat paw oedema

30 Eight week old male Lewis rats were used for this experiment. The paw oedema was induced by the injection of 100µl of 0.1% lambda carrageenin (Sigma type 4 (C3889)) dissolved in 0.9% saline in each paw.

- 15 -

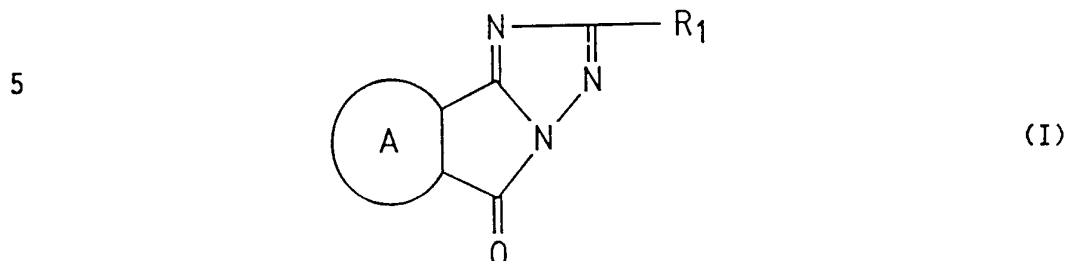
The test compound, 2-phenyl-5H-1,2,4-triazolo[5,1-a]isoindol-5-one was administered orally one hour before the induction of the paw oedema. The compound was given in the dose 200 μ mol/kg/body weight and a control drug, Piroxicam was used as
5 a positive reference in the concentration 30 μ moles per kg of body weight. There was also a control group who were not treated.

The resultant paw swelling was then measured over the next 4 hours. Piroxicam reduced the rat paw oedema in the manner described in the literature. The reduction for the test compound
10 drug was calculated from a control group. It was found that the compound reduced the oedema up to a level of 20%.

- 16 -

CLAIMS

1. A compound of the general formula (I) below

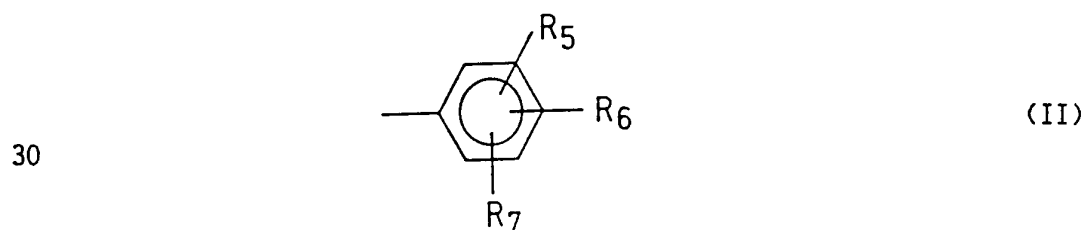


10 wherein A is

- 1,2-phenylene, optionally mono- or di-substituted by an alkyl group of 1-4 carbon atoms, an alkoxy group of 1-4 carbon atoms, CF₃, halogen, OH or NR₂R₃ wherein R₂ and R₃ which may be the same or different are H or an alkyl group of 1-4 carbon atoms,
- 15 - 4-cyclohexen-cis-1,2-ylene
- 1-cyclohexen-1,2-ylene
- cis-1,2-cyclohexylene

and R₁ is

- 20 - a 5 or 6 membered heterocyclic ring containing one or two of the heteroatoms N, O and S, optionally mono-or di-substituted by an alkyl group of 1-4 carbon atoms an alkoxy group of 1-4 carbon atoms, halogen, or OH
- a cyclohexyl group
- 25 - a group of formula (II) below



35

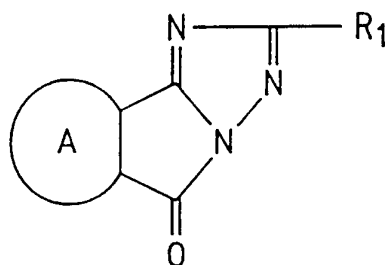
- 17 -

wherein R_5 , R_6 and R_7 which may be the same or different are H, OH, an alkyl group of 1-4 carbon atoms, an alkoxy group of 1-4 carbon atoms, CF_3 , halogen or the group NR_2R_3 wherein R_2 and R_3 are as defined above,

- 5 the compound optionally being in the form of a pharmaceutically acceptable pro-drug formed at one or more hydroxy groups in a substituted 1,2-phenylene group A and/or a substituted group R_1 for use in therapy.

2. A compound of the general formula (I) below

10



(I)

15

wherein A is

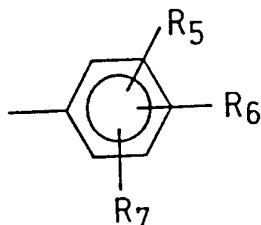
- 1,2-phenylene, optionally mono- or di-substituted by an alkyl group of 1-4 carbon atoms, an alkoxy group of 1-4 carbon atoms, CF_3 , halogen, OH or NR_2R_3 wherein R_2 and R_3 which may be the same or different are H or an alkyl group of 1-4 carbon atoms,
- 4-cyclohexen-cis-1,2-ylene
- 25 - 1-cyclohexen-1,2-ylene
- cis-1,2-cyclohexylene

and R_1 is

- a 5 or 6 membered heterocyclic ring containing one or two of the heteroatoms N, O and S, optionally mono- or di-substituted by an alkyl group of 1-4 carbon atoms, an alkoxy group of 1-4 carbon atoms, halogen, or OH
- 30 - a cyclohexyl group
- a group of formula (II) below

- 18 -

5



(II)

10 wherein R_5 , R_6 and R_7 which may be the same or different are H, OH, an alkyl group of 1-4 carbon atoms, an alkoxy group of 1-4 carbon atoms, CF_3 , halogen or the group NR_2R_3 wherein R_2 and R_3 are as defined above,

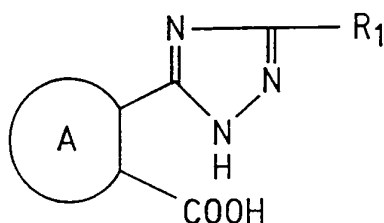
15 the compound optionally being in the form of a pharmaceutically acceptable pro-drug formed at one or more hydroxy groups in a substituted 1,2-phenylene group A and/or in a substituted group R_1 with the proviso that A cannot be 1,2-phenylene when R_1 is phenyl.

20 3. A compound according to claim 1 or 2 in which R_1 is a substituted or unsubstituted pyridyl, pyrazinyl, furyl, thienyl, or phenyl group.

4. A compound according to claim 1 which is 2-phenyl-5H-1,2,4-triazolo[5,1-a]isindol-5-one.

25 5. A method of preparation of compounds as claimed in claim 2 comprising the cyclization of a compound of general formula (III).

30



(III)

wherein A and R_1 are as defined in claim 2.

- 19 -

6. A pharmaceutical composition comprising a compound according to claim 1, 2, 3 or 4 in admixture with a pharmaceutically acceptable diluent or carrier.
7. A pharmaceutical composition according to claim 6 adapted for oral administration.
8. A pharmaceutical composition according to claim 6 adapted for parenteral administration.
9. A pharmaceutical composition according to claim 6, 7 or 8 in dosage unit form.
10. A method of treating chronic inflammatory disease in a subject in need of such treatment which comprises administering to said subject a therapeutically effective amount of a compound according to claim 1.
11. Use of a compound according to claim 1 for the manufacture of a medicament for use in the treatment of chronic inflammatory disease.
12. A method according to claim 10 or use according to claim 11 characterised in that the amount of compounds administered is from, 0.01mg/kg to 20mg/kg body weight.
13. A method or use according to claim 12 characterised in that the amount of compound administered is from 0.04mg/kg to 10mg/kg body weight.
14. A method according to claim 10 or a use according to claim 11 characterised in that the chronic inflammatory disease is psoriasis, rheumatoid arthritis or inflammatory bowel disease.

INTERNATIONAL SEARCH REPORT

Internat' Application No
PCT/IB 94/00010

A. CLASSIFICATION OF SUBJECT MATTER

IPC 5 C07D487/04 A61K31/41 C07D403/14 A61K31/44 C07D405/14

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)

IPC 5 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)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US,A,3 895 113 (OMODEI-SALE) 15 July 1975 cited in the application ---	1-9
A	US,A,4 007 276 (OMODEI-SALE) 8 February 1977 cited in the application see column 2, line 14; claim 1 --- -/--	1-9

☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents :

- *A* document defining the general state of the art which is not considered to be of particular relevance
- *E* earlier document but published on or after the international filing date
- *L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- *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

30 March 1994

Date of mailing of the international search report

28.04.94

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel. (+ 31-70) 340-2040, Tx. 31 651 epo nl,
Fax: (+ 31-70) 340-3016

Authorized officer

Gettins, M

INTERNATIONAL SEARCH REPORT

Internat' Application No
PCT/IB 94/00010

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	CHEMICAL ABSTRACTS, vol. 86, no. 5, 31 January 1977, Columbus, Ohio, US; abstract no. 29720w, KORSHAK 'Synthesis and study of heterocyclic systems based on benzamidrazone.' page 360 ;column 1 ; cited in the application & IZV. AKAD. NAUK GRUZ. SSR, SER. KHIM vol. 2, no. 2 , 1976 pages 103 - 108 ---	1-9
A	CHEMICAL ABSTRACTS, vol. 109, no. 21, 21 November 1988, Columbus, Ohio, US; abstract no. 190324y, MEHTA 'Reactions of cyclic anhydrides with thiosemicarbazide.' page 705 ;column 2 ; see abstract & INDIAN J. CHEM., SECT. B, vol. 26B, no. 12 , 1987 pages 1130 - 1132 -----	1-9

INTERNATIONAL SEARCH REPORT

Information on patent family members

Internat	Application No
PCT/IB 94/00010	

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US-A-3895113	15-00-00	GB-A- 1477302	22-06-77
		GB-A- 1477303	22-06-77
		AT-B- 334370	10-01-76
		AT-B- 334371	10-01-76
		AU-A- 6881474	13-11-75
		AU-A- 6881774	13-11-75
		AU-A- 6881974	13-11-75
		BE-A- 815497	16-09-74
		BE-A- 815498	16-09-74
		BE-A- 815499	16-09-74
		CA-A- 1024892	24-01-78
		CA-A- 1030540	02-05-78
		CA-A- 1044237	12-12-78
		CH-A- 593693	15-12-77
		CH-A- 603166	15-08-78
		CH-A- 596208	15-03-78
		CH-A- 603641	31-08-78
		DE-A, C 2424572	12-12-74
		DE-A, C 2424670	12-12-74
		DE-A, B, C 2424671	12-12-74
		DE-C- 2463023	11-10-84
		FR-A, B 2230369	20-12-74
		FR-A, B 2241292	21-03-75
		FR-A, B 2241293	21-03-75
		FR-A, B 2262517	26-09-75
		JP-C- 957162	14-06-79
		JP-A- 50035193	03-04-75
		JP-B- 53037877	12-10-78
		JP-C- 935248	30-11-78
		JP-A- 50035195	03-04-75
		JP-B- 53015078	22-05-78
		LU-A- 70150	09-10-74
		LU-A- 70151	09-10-74
		NL-A- 7406994	27-11-74
		NL-A- 7406995	27-11-74
		NL-A- 7801129	31-05-78
		SE-B- 419542	10-08-81
		SE-B- 419543	10-08-81
		SE-B- 434642	06-08-84
		SE-A- 7710485	19-09-77

INTERNATIONAL SEARCH REPORT

Information on patent family members

Internal Application No

PCT/IB 94/00010

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US-A-3895113		US-E- RE30456 US-A- 4007276	23-12-80 08-02-77

US-A-4007276	08-00-00	GB-A- 1477302 AT-B- 334370 AT-B- 334371 AU-A- 6881474 AU-A- 6881774 AU-A- 6881974 BE-A- 815497 BE-A- 815498 BE-A- 815499 CA-A- 1024892 CA-A- 1030540 CA-A- 1044237 CH-A- 593693 CH-A- 603166 CH-A- 596208 CH-A- 603641 DE-A, C 2424572 DE-A, C 2424670 DE-A, B, C 2424671 DE-C- 2463023 FR-A, B 2230369 FR-A, B 2241292 FR-A, B 2241293 FR-A, B 2262517 JP-C- 957162 JP-A- 50035193 JP-B- 53037877 JP-C- 935248 JP-A- 50035195 JP-B- 53015078 LU-A- 70150 LU-A- 70151 NL-A- 7406994 NL-A- 7406995 NL-A- 7801129 SE-B- 419542 SE-B- 419543	22-06-77 10-01-76 10-01-76 13-11-75 13-11-75 13-11-75 16-09-74 16-09-74 16-09-74 24-01-78 02-05-78 12-12-78 15-12-77 15-08-78 15-03-78 31-08-78 12-12-74 12-12-74 12-12-74 11-10-84 20-12-74 21-03-75 21-03-75 26-09-75 14-06-79 03-04-75 12-10-78 30-11-78 03-04-75 22-05-78 09-10-74 09-10-74 27-11-74 27-11-74 31-05-78 10-08-81 10-08-81

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/IB 94/00010

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US-A-4007276		SE-B- 434642	06-08-84
		SE-A- 7710485	19-09-77
		US-E- RE30456	23-12-80
		US-A- 3895113	15-07-75
