

PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

PCT

WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY
(PCT Rule 43*bis*.1)

To:

see form PCT/ISA/220

Date of mailing
(day/month/year) see form PCT/ISA/210 (second sheet)

Applicant's or agent's file reference
see form PCT/ISA/220

FOR FURTHER ACTION
See paragraph 2 below

International application No.
PCT/GB2006/002344

International filing date (day/month/year)
27.06.2006

Priority date (day/month/year)
28.06.2005

International Patent Classification (IPC) or both national classification and IPC
INV. C07D413/12 C07D417/12 C07D403/12 A61K31/506 A61P5/02

Applicant
PARADIGM THERAPEUTICS LTD.

1. This opinion contains indications relating to the following items:

- Box No. I Basis of the opinion
- Box No. II Priority
- Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- Box No. IV Lack of unity of invention
- Box No. V Reasoned statement under Rule 43*bis*.1 (a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- Box No. VI Certain documents cited
- Box No. VII Certain defects in the international application
- Box No. VIII Certain observations on the international application

2. **FURTHER ACTION**

If a demand for international preliminary examination is made, this opinion will usually be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA") except that this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notified the International Bureau under Rule 66.1*bis*(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of 3 months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

Name and mailing address of the ISA:



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Date of completion of
this opinion

see form
PCT/ISA/210

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**WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY**

International application No.
PCT/GB2006/002344

Box No. I Basis of the opinion

1. With regard to the **language**, this opinion has been established on the basis of:
 - the international application in the language in which it was filed
 - a translation of the international application into , which is the language of a translation furnished for the purposes of international search (Rules 12.3(a) and 23.1 (b)).
2. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application and necessary to the claimed invention, this opinion has been established on the basis of:
 - a. type of material:
 - a sequence listing
 - table(s) related to the sequence listing
 - b. format of material:
 - on paper
 - in electronic form
 - c. time of filing/furnishing:
 - contained in the international application as filed.
 - filed together with the international application in electronic form.
 - furnished subsequently to this Authority for the purposes of search.
3. In addition, in the case that more than one version or copy of a sequence listing and/or table relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.
4. Additional comments:

Box No. II Priority

1. The validity of the priority claim has not been considered because the International Searching Authority does not have in its possession a copy of the earlier application whose priority has been claimed or, where required, a translation of that earlier application. This opinion has nevertheless been established on the assumption that the relevant date (Rules 43*bis*.1 and 64.1) is the claimed priority date.
2. This opinion has been established as if no priority had been claimed due to the fact that the priority claim has been found invalid (Rules 43*bis*.1 and 64.1). Thus for the purposes of this opinion, the international filing date indicated above is considered to be the relevant date.
3. Additional observations, if necessary:

**WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY**

International application No.
PCT/GB2006/002344

Box No. V Reasoned statement under Rule 43bis.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes: Claims	1-24
	No: Claims	
Inventive step (IS)	Yes: Claims	
	No: Claims	1-24
Industrial applicability (IA)	Yes: Claims	1-24
	No: Claims	

2. Citations and explanations

see separate sheet

Box No. VII Certain defects in the international application

The following defects in the form or contents of the international application have been noted: .

see separate sheet

Box No. VIII Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

see separate sheet

V. CITATIONS AND EXPLANATIONS

The following documents are mentioned in this Written Opinion.

EP-A-1,334,972	(A)
WO-A-2005 005442	(B)
WO-A-00 20358	(C)

The novel structural feature of the compounds of claim 1 is the presence of at least two heteroatoms in Ring 1, as well as the presence of the groups "Y" and "Z" on the phenyl group, which represent other than silicon containing groups. The dependent claims 2-15, as well as claim 16 drawn to compounds of claim 1 for use in therapy, claim 17 drawn to pharmaceutical compositions containing compounds of claim 1, and claims 18-24 drawn to the use of compounds of claim 1 for the preparation of medicaments are novel by consequence. Claims 1 to 24 therefore meet the Novelty requirements of Article 33(2) PCT.

Document (B) describes 2-(pyrimidin-4-yl)-aminocarbonyl-5-phenoxy-furans in which the phenyl group is substituted by a trialkyl moiety (see examples). The compounds are useful as GnRH antagonists. Document (C) discloses several 2-phenylmethyl-5-(aryl- or heteroaryl)-aminocarbonyl-furans as GnRH antagonists. Further examples in which the heteroaryl group is pyrimidinyl are disclosed in document (A). These compounds do not have silyl substituents. From claim 10 of this document it is suggested that the five membered heteroaryl ring preferably contains 2 or 3 heteroatoms. Thus the skilled man would expect to arrive at further GnRH antagonists by replacing the furan ring in the examples of (C) with heteroaryl ring such as oxazole and thiazole. Since it is also taught in document (B) that the phenyl group can be bound to Ring 1 by O, S(O)_m or CH₂, the skilled man would also expect that replacing the benzyl group in formula I of claim 10 by phenoxy would lead to further GnRH antagonists.

Thus it appears that the presently claimed compounds have a combination of substituents for D-G and "Ring 1" which are each individually known to be active in GnRH antagonists. Consequently, inventive step (Article 33(3) PCT) cannot be recognised because the problem of making available further GnRH antagonists appears to have been solved in an

obvious manner. Inventive step for the presently claimed compounds could be recognised if the Applicant could demonstrate an unexpected effect in comparison with the closest prior art compounds (e.g. from document (A)). The applicant is requested to submit further information and argumentation in order to make credible the involvement of inventive step for the presently claimed compounds.

VII. CERTAIN DEFECTS IN THE INTERNATIONAL APPLICATION

In order to meet the requirements of Rule 5.1(a)(ii) PCT, documents (A) and (B) should be identified in the description and the relevant prior art disclosed therein should be briefly discussed.

VIII. CERTAIN OBSERVATIONS ON THE INTERNATIONAL APPLICATION

Due to the very broad scope of the substituents included in the definitions of "Ring 1", "Ring 2", E-G and J-L, it was not possible to carry out a complete structural search within a reasonable time. The structure search was therefore limited to the scope embraced by the worked examples (see Guidelines, B-III, 3.7).