Handbook 9

LGD 1550

1. Chemical and Physical Characteristics

1.1 Nomenclature

See note on nomenclature of retinoids in the General Remarks, section 1.4.

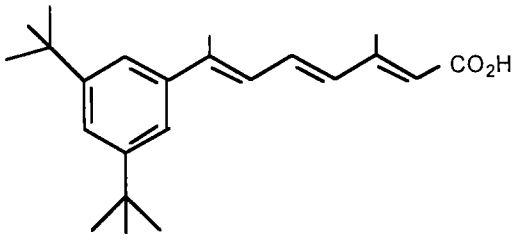
1.2 Name

Chemical Abstracts Services Registry Number
178600-20-9

IUPAC systematic name
(all-*E*)-7-[3,5-Bis(1,1-dimethylethyl)phenyl]-3-methyl-2,4,6-octatrienoic acid

Synonyms
AGN 193101; ALRT 1550; ALRT1550; all-*trans*-7-[3,5-bis-1,1-dimethylethyl)phenyl]-3-methyl-2,4,6-octatrienoic acid; (2*E*,4*E*,6*E*)-7-(3,5-di-*tert*-butylphenyl)-3-methyl-2,4,6-octatrienoic acid; (2*E*,4*E*,6*E*)-7-(3,5-di-*tert*-butylphenyl)-3-methylocta-2,4,6-trienoic acid, (*E*)-7-(3,5-di-*tert*-butylphenyl)-3-methyl-2,4,6-octatrienoic acid; LG1550; LGD100550

1.3 Structural formula



Composition: $C_{23}H_{32}O_2$
Relative molecular mass: 340.24

1.4 Physical and chemical properties

Appearance
Pale-yellow needles

Melting point
196–198 °C

Spectroscopy
^{1}H-NMR ($CDCl_3$): δ 1.35 (s, 18H, 6 CH_3), 222.29 (s, 3H, CH_3), 2.41 (s, 3H, CH_3), 5.84 (s, 1H, C=CH), 6.41 (d, J = 15 Hz, 1H, C=CH), 6.54 (d, J = 11 Hz, 1H, C=CHO, 7.08 (m, 1H, C=CH), 7.32 (d, J = 1 Hz, 2H, ArH), 7.39 (t, J = 1 Hz, 1H, ArH)

High-resolution mass spectrum
Calculated for $C_{23}H_{32}O_2$, 340.2402, found 340.2394 (see Zhang *et al.*, 1996)

Solubility
Soluble in organic solvents (see all-*trans*-Retinoic acid, section 1.4)

Stability
Unstable to light, oxygen and heat (see all-*trans*-Retinoic acid, section 1.4)

2. Occurrence, Production, Use, Human Exposure and Analysis

2.1 Occurrence

LGD 1550 is a synthetic drug, and human exposure is limited to patients receiving it.

2.2 Production

LGD 1550 was prepared in five steps from 3,5-di-*tert*-benzoic acid, as shown in Figure 1 (Zhang *et al.*, 1996).

2.3 Use

Phase-I/II trials of the use of LGD 1550 in combination with cisplatin and radiation for head-and-neck cancer, in combination with chemotherapy for ovarian cancer and in combination with interferon for advanced cervical cancer are under way.

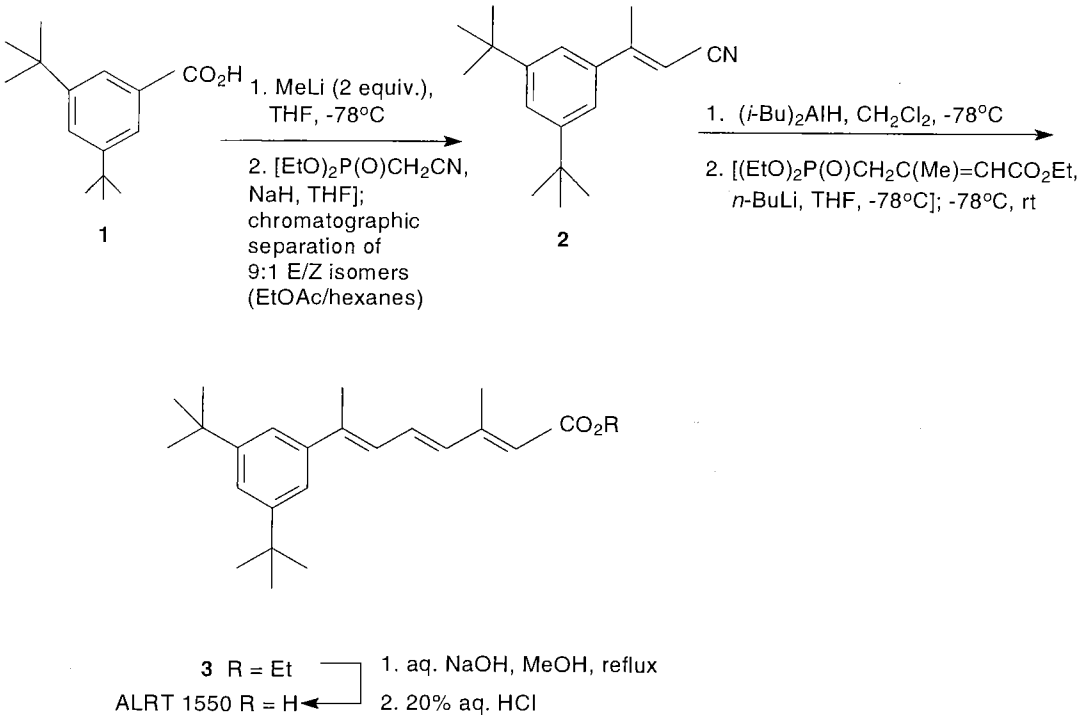


Figure 1. Synthesis of LGD 1550

2.4 Human exposure

LGD 1550 is being tested in phase-I/II trials for cancer therapy.

2.5 Analysis

LGD 1550 can be separated by thin-layer chromatography (10% methanol and 90% chloroform): R_f 0.6 (Zhang *et al.*, 1996). High-performance liquid chromatography has also been used for analysis of this retinoid (Howell *et al.*, 1998).

3. Metabolism, Kinetics and Genetic Variation

3.1 Humans

A phase-I/II study indicated a plasma half-life for LGD 1550 of 5 h. The concentrations in plasma were similar on days 1, 15 and 29, as determined from the integrated areas under the curves of concentration–time, indicating that the clearance of LGD 1550 is not self-induced (Soignet *et al.*, 1998).

3.2 Experimental models

The metabolites of LGD 1550 formed by rat liver microsomes, although not identified, are presumed to be mono-hydroxylated or acyl-glucuronidated structures (Howell *et al.*, 1998).

4. Cancer-preventive Effects

4.1 Humans

No data were available to the Working Group.

4.2 Experimental models

4.2.1 Cancer and preneoplastic lesions

No data were available to the Working Group.

4.2.2 Intermediate biomarkers

No data were available to the Working Group.

4.2.3 *In-vitro models*

4.2.3.1 *Cellular studies*

These studies are summarized in Table 1.

LGD 1550 dissolved in 10% dimethylsulfoxide and 90% ethanol was studied for antiproliferative activity by addition for four days to a culture of the human cervical carcinoma cell line ME180. Incorporation of radioactive thymidine was then measured over a concentration of 10^{-12}–10^{-6} mol/L. LGD 1550 was active, with a median inhibitory concentration of 1 nmol/L, whereas all-*trans*-retinoic acid was active under the same assay conditions only at 300 nmol/L. The activity of LGD 1550 correlated with its increased ability to activate retinoic acid receptors (Zhang *et al.*, 1996).

LGD 1550 potently inhibited proliferation of human breast cancer cell lines, irrespective of their oestrogen-receptor status. The activity correlated with expression of RARα. In responsive cells such as T-47 D, SK-BR-3 and HS 578T, LGD 1550 was significantly more active than 9-*cis*-retinoic acid, LGD 1550 having a median effective concentration of 1–4 nmol/L (Fitzgerald *et al.*, 1997).

In a study reported only in an abstract, the antiproliferative effect of LGD 1550 was examined in UMCSS-22B cells from a human head-and-neck carcinoma. The median inhibitory concentration with continuous exposure was stated to be 0.22 nmol/L [method for determining proliferation not stated]. LGD 1550 acted synergistically with interferon and cisplatin in this assay (Shalinsky *et al.*, 1996).

4.2.3.2 *Antimutagenicity in short-term tests*

No data were available to the Working Group.

4.3 Mechanisms of cancer prevention

Some of the biological effects of LGD 1550 may be mediated by its selective binding to retinoic acid receptors (RARs). Table 2 shows the relative binding affinity of LGD 1550 to the RARs and retinoid X

Table 1. Antiproliferative activity of LGD 1550

End-point	Assay	Result	Potency (IC_{50}; nmol/L)	Comments	Reference
Proliferation (^{3}H-thymidine incorporation)	ME180 cervical carcinoma cells	Active	1	300 times more potent than all-*trans*-retinoic acid	Zhang *et al.* (1996)
Proliferation	Head-and-neck squamous carcinoma cells	Active	0.22	370 times more potent than 9-*cis*-retinoic acid Potentiates activity of interferon	Shalinsky *et al.* (1996)

IC_{50}, concentration that inhibits proliferation by 50%

Table 2. Relative binding affinity of LGD 1550 to retinoic acid receptors (RARs) and retinoid X receptors (RXRs)

Receptor	Relative binding affinity	EC_{50} (nmol/L)
RARα	1.1	4.0
RARβ	0.7	2.2
RARγ	1.9	0.3
RXRα	224	> 1000
RXRβ	560	> 1000
RXRγ	320	> 1000

From Shalinsky *et al.* (1996) and Zhang *et al.* (1996). EC_{50}, median effective concentration. The results are an average of four or five experiments with triplicate determinations.

receptors (RXRs). LGD 1550 binds to the RARs 100–800 times more potently than to RXRs (Zhang *et al.*, 1996; Shalinsky *et al.*, 1997). Table 2 also shows the results of co-transfection assays (Shalinsky *et al.*, 1997), which measure the capacity of compounds to activate gene expression through each of the six known retinoid receptors. LGD 1550, with a median effective concentration of 0.3–4 nmol/L, was > 250 times more active with the RARs than with the RXRs. In both the binding and the co-transfection assays, LGD 1550 was > 10 times more potent than all-*trans*-retinoic acid.

5. Other Beneficial Effects

No data were available to the Working Group.

6. Carcinogenicity

No data were available to the Working Group.

7. Other Toxic Effects

7.1 Adverse effects

7.1.1 Humans

No data were available to the Working Group.

7.1.2 Experimental models

Athymic nude mice, six to seven weeks of age, received LGD 1550 in sesame oil by oral intubation at daily doses of 0, 3, 10, 30, 50 or 100 µg/kg bw, five days per week for up to eight weeks. The compound was well tolerated at doses up to 10 µg/kg bw per day, but there was a dose-dependent reduction in body-weight gain with increasing dose. Mice at 100 µg/kg bw per day lost about 25% of their body weight and were killed on day 11. Mild, moderate and severe mucocutaneous irritation occurred at 30, 50 and 75 µg/kg bw per day, respectively. The maximum tolerated oral dose was 50 µg/kg bw per day (Shalinsky *et al* 1997).

7.2 Reproductive and developmental effects

No data were available to the Working Group.

7.3 Genetic and related effects

No data were available to the Working Group.

8. Summary of Data

8.1 Chemistry, occurrence and human exposure

LGD 1550 (all-*trans*-7-[3,5-bis(1,1-dimethylethyl)-phenyl]-3-methyl-2,4,6-octatrienoic acid) is a synthetic aromatic retinoid that is structurally related to all-*trans*-retinoic acid. Because of its conjugated triene structure, LGD 1550 has a characteristic absorption in the ultraviolet and visible spectrum and can readily photoisomerize in solution to multiple geometric isomers. Human exposure is limited to patients undergoing clinical trials.

8.2 Metabolism and kinetics

Few data are available.

8.3 Cancer-preventive effects

8.3.1 Humans

No data were available to the Working Group.

8.3.2 Experimental models

No data were available to the Working Group. LGD 1550 inhibited proliferation of human breast cancer cells that express retinoic acid receptor-α, but not in cells that did not express this receptor.

8.3.3 Mechanisms of cancer prevention

There were insufficient data to determine the mechanism of action of LGD 1550.

8.4 Other beneficial effects

No data were available to the Working Group.

8.5 Carcinogenicity

No data were available to the Working Group.

8.6 Other toxic effects

8.6.1 Humans

No data were available to the Working Group.

8.6.2 Experimental models

In one study, short-term administration of LGD 1550 to athymic nude mice induced mucocutaneous irritation. No data were available on the reproductive or developmental effects of LGD 1550 in experimental animals, or on its genetic effects in short-term assays.

9. Recommendations for research

9.1 General recommendations for LGD 1550 and other retinoids

See section 9 of the Handbook on all-*trans*-retinoic acid.

9.2 Recommendations specific to LGD 1550

None.

10. Evaluation

10.1 Cancer-preventive activity

10.1.1 Humans

There is *inadequate evidence* that LGD 1550 has cancer-preventive activity in humans.

10.1.2 Experimental animals

There is *inadequate evidence* that LGD 1550 has cancer-preventive activity in experimental animals.

10.2 Overall evaluation

There are no data on the cancer-preventive activity of LGD 1550 in humans.

11. References

Fitzgerald, P., Teng, M., Chandraratna, R.A., Heyman, R.A. & Allegretto, E.A. (1997) Retinoic acid receptor α expression correlates with retinoid-induced growth inhibition of human breast cancer cells regardless of estrogen receptor status. *Cancer Res.*, **57**, 2642–2650

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