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Act. 523 RESPUESTA

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08-105545

Patente de Invención:

**“COMBINACION FARMACEUTICA QUE
COMPRENDE 3-(3-DIMETIL-AMINO-1-
ETIL-2-METILPROPIL)-FENOL Y
PARACETAMOL”**

Solicitud Internacional No. **PCT/EP2007/003632**

Clasificación Internacional: **A61K 31/137 // 31/167 y A61P29/00**

Titular:

GRUNENTHAL GMBH

RESPUESTA A REQUERIMIENTO ARTÍCULO 45

OFICIO No. 12538 NOTIFICADO POR ESTADO DE 18 DE JULIO DE 2012.

HUMBERTO RUBIO CAMACHO, mayor de edad, domiciliado en Bogotá, D.C., identificado con la cédula de ciudadanía número 17'192.062 de Bogotá, abogado graduado portador de la Tarjeta Profesional No. 50.007 expedida por el Consejo Superior de la Judicatura, actuando en carácter de Apoderado de **GRUNENTHAL GMBH**, domiciliado en Zieglerstrasse 6, 52078 Aachen, Alemania; encontrándome dentro de la debida oportunidad procesal para dar respuesta al auto proferido por su Despacho, mediante Oficio 12538, notificado por fijación en lista 18 de julio de 2012 y de acuerdo a la solicitud de prorroga radicada a su Despacho el 8 de Octubre de 2012, me permito:

Manifiestar:

I. En el informe emitido sobre la presente invención, se han formulado las objeciones que a continuación resumimos:

1.- Excepción a la Patentabilidad (Art 20 D 486 literal (d))

El objeto de las reivindicaciones 8-11 no es patentable de acuerdo con el Artículo citado.

2.- Reivindicaciones relativas a un uso o a un segundo uso (Art 14 y 21 D 486)

El uso de las reivindicaciones 12-13 no es patentable, de acuerdo con el Art. 14.

3. Reivindicaciones (Art 30 D 486, Art 22 PCT)

- La reivindicación 1 no es clara porque la expresión “Paracetamol o derivado del mismo” no es limitativa y es impreciso, por lo cual no permite distinguir la invención del estado de la técnica.

- La reivindicación 5 no esta sustentada en la Descripción porque la característica “en que el derivado de paracetamol es seleccionado de un compuesto por paracetamol y fenidina” esta en la reivindicación y no en la descripción. Se sugiere incorporarla a la descripción para dar soporte.

- La reivindicación 11 no esta sustentada en la Descripción porque la característica “Porque adicionalmente abarca cafeína” esta en la reivindicación y no en la descripción, adicionalmente no era parte del objeto inicial de la solicitud inicial. Se sugiere excluir.

- Se sugiere realizar la modificación del encabezado de las reivindicaciones 1-6 indicándolas en forma de composición farmacéutica y no de combinación.

4. Descripción (Art 28 D486)

Hay una inconsistencia entre el estado del arte y la descripción en lo referente “en la conversión del acido ara clorhídrico.

5. Determinación del Estado de la Técnica

El estado de la técnica se determino con base en la fecha de presentación de la solicitud de prioridad 28 de abril de 2006 y se encontraron los siguientes documentos que anticipan el objeto de esta solicitud:

Ítem	Documento	Titulo	Fecha de Publicación
D1	Anesthesia Progress 2001 Summer; 48(3) 79-81	Tramadol and acetaminophen tablets for dental pain	2001
D2	ES 2115298	Nuevos derivados	16/junio/1998

		del 1 fenil-3-metil-amino-propano, su proceso de fabricación y las composiciones que los contienen	
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6. Examen de Patentabilidad (Art 14 D486)
Novedad

- La reivindicación 1 consiste en una combinación farmacéutica de dos analgésicos que comprende por lo menos un isómero 3-(3-dimetilamino-1-etil-2-2-metil-propil)fenol y paracetamol o sus derivados.
- El documento D1 se considera el estado de la técnica cercano a la invención definida en la reivindicación 1 porque divulgan una combinación farmacéutica dos analgésicos que comprende como componentes paracetamol y otro analgésico.
- La diferencia entre la invención y la definida en la reivindicación 1 y el documento D2 es que la invención indica una combinación farmaceutica entre el paracetamol y un isómero del compuesto (3-(3dimetilamino-1-etil-2-metil-propil)-fenol y el documento D2 no indica o sugiere la combinación de los compuestos de la invención con otros analgésicos.
- En consecuencia la persona del oficio normalmente versada en la materia, tendría suficiente motivación para remplazar el analgésico tramadol en la combinación farmacéutica divulgada en el D1 de la manera como lo indica el documento D2 para llegar así al objeto de la reivindicación 1 de la solicitud. Por lo cual se considera obvia.

Conclusión:

La reivindicación 1 cumple el requisito de novedad (Art 16), pero no cumple con el requisito e nivel inventivo (Art 18).

7. Conclusión

Los requisitos de Patentabilidad de la presente solicitud están afectados asi:

Item	Documento	Reivindicaciones afectadas	Requisito que afecta
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D1	Anesthesia progress, 2001 summer, 48(3): 79- 81	1-11	Nivel Inventivo
D2	ES 2115298	1-11	Nivel Inventivo

II.- En contestación a las observaciones anteriores, manifestamos lo siguiente:

a) De las Reivindicaciones

- Se anexa un nuevo capitulo reivindicatorio (1-3) Teniendo en cuenta las observaciones expuestas por el examinador, en la acción oficial, se han corregido las reivindicaciones de forma que definan y precisen de manera clara y concisa el objeto y la materia reclamada. Adicionalmente, nos permitimos informar que las modificaciones realizadas a las reivindicaciones están enteramente sustentadas en la memoria descriptiva de la presente solicitud y no contienen materia que no haya sido incluida anteriormente, es decir no incluye materia nueva.
- En primer lugar, se han enmendado las reivindicaciones de modo que se describe una “combinación farmacéutica” en lugar de una “combinación”, tal como ha sido sugerido por el examinador.
- Para superar las objeciones por falta de claridad, se ha eliminado la expresión “o un derivado del mismo” de la reivindicación 1, por lo que se ha eliminado la reivindicación original 5 por ser dependiente de tal característica, dando por superada además la falta de sustento objetada a esta última reivindicación.
- Además, la reivindicación principal ha sido limitada de acuerdo a la antigua reivindicación 4, restringiendo el compuesto (a) a los compuestos (1R, 2R)-3-(3-Dimetilamino-1-etil-2-metil-propil)-fenol de la formula (I') o una adición de sal de ácido de ello, donde en la adición de sal de ácido se prefiere el hidrocloreuro. Por lo tanto, se han eliminado las antiguas reivindicaciones 2 y 3 por ser redundantes en vista de la reivindicación a la reivindicación principal.

- Se han eliminado las reivindicaciones afectadas por exclusión de patentabilidad y las relativas a uso y segundo uso, correspondientes a las reivindicaciones originales 8 a 13. De tal forma también se supera la objeción que recaía sobre la reivindicación original 11 que no tendría sustento.

b) Del Capítulo Descriptivo

Respecto a la inconsistencia indicada en la memoria descriptiva, en referencia a la “conversión del ácido ara clorhídrico” se hace presente que corresponde a un error de traducción y el compuesto correcto es el “ácido araquidónico”, por lo que se ha hecho la corrección correspondiente en la memoria descriptiva.

c) Nivel Inventivo:

- El examinador rechaza la presente invención por falta de nivel inventivo en vista de **D1** (Medve et al.) y **D2** (ES2115298T3 correspondiente a DE4426245A1, citado en el Reporte de Búsqueda Internacional de la presente solicitud PCT).

- El solicitante hace presente respetuosamente que no está de acuerdo con lo indicado por el examinador en cuanto a que debido a que D1 divulga una combinación de tramadol y acetaminofén (paracetamol), habría sido obvio reemplazar el tramadol por (1R,2R)-3-(3-Dimetilamino-1-etil-2-metil-propil)-fenol para mejorar la actividad analgésica del paracetamol y así reducir los efectos secundarios de la composición al remover el tramadol.

- D2 por su parte se relaciona con derivados de 1-fenil-3-dimetilamino-propano con actividad farmacológica.

- Estos compuestos ejercen un efecto analgésico y son apropiados para el tratamiento del dolor severo sin aumentar los efectos secundarios conocidos de los opioides y que no deberían exhibir los efectos secundarios que ocurren en algunos casos con el tratamiento con tramadol, por ejemplo, náusea y vómito (ver D2, pág 2, líneas 34-38). Los compuestos se distinguen por un marcado efecto analgésico, que es significativamente más intenso comparado con el tramadol (D2, pág. 2, líneas 39-42) y que pueden ser usados como ingredientes activos en las drogas, preferentemente como

ingredientes activos en drogas para combatir el dolor. D2 divulga la elaboración de (1R,2R)-3-(3-Dimetilamino-1-etil-2-metil-propil)-fenol (D2, Ejemplo 24).

- Un objetivo de la presente invención es encontrar una combinación farmacéutica que sea apropiada para el tratamiento del dolor y que de preferencia exhiba menores efectos secundarios comparados con los que provocan sus componentes individuales, al ser administrados en dosis efectivas.

- Sorprendentemente, los inventores de la presente invención, han obtenido que una composición farmacéutica de (1R,2R)-3-(3-Dimetilamino-1-etil-2-metil-propil)-fenol y paracetamol muestra un efecto sinérgico (supra-aditivo).

- Una persona experta en la técnica está en conocimiento que dos drogas pueden o no interactuar entre ellas al ser administradas a un paciente. Si ocurre la interacción, esta puede ser negativa, por ejemplo, en cuanto a la toxicidad. Sin embargo, la interacción podría conducir a un efecto aditivo o, incluso, a un efecto supra-aditivo.

- Un efecto supra-aditivo se observa cuando las drogas interactúan en una forma que aumenta o magnifica uno o más de los efectos que provocan esas drogas.

- En cualquier caso, el comportamiento global de la combinación de dos o más drogas al ser administradas a un paciente no puede ser predicho a partir del comportamiento de sus componentes individuales. La capacidad que tienen dos drogas de mostrar un efecto supra-aditivo es determinada a partir de sus propiedades farmacológicas y farmacocinéticas y es, por ejemplo, una función de las características fisicoquímicas de los compuestos de la droga y de sus modos de acción dentro del cuerpo del paciente. En consecuencia, se requieren análisis farmacológicos completos para evaluar si determinada combinación de drogas muestra una interacción favorable e incluso un posible efecto supra-aditivo.

- Una vez que obtiene que cierta combinación de drogas interactúa favorablemente con otra, podría ser razonable para alguien experto en la materia el intercambiar uno de estas drogas por otra que tenga propiedades fisicoquímicas similares, por ejemplo, con una estructura molecular similar, y que ejerza sus efectos beneficiosos a través del mismo modo de acción, es decir, a través del mismo receptor, lo que llevaría a obtener una combinación de drogas que muestre la misma interacción positiva al ser administradas.

- D2 no da indicios de que los compuestos divulgados puedan ser usados en combinación con paracetamol, ni tampoco que una composición que comprende (1R,2R)-3-(3-Dimetilamino-1-etil-2-metil-propil)-fenol y paracetamol pueda dar resultado a un efecto sinérgico (supra-aditivo).

- D1 no hace referencias al compuesto (1R,2R)-3-(3-Dimetilamino-1-etil-2-metil-propil)-fenol, y mucho menos hace referencia a que tal compuesto pueda ser combinado con paracetamol o tramadol.

- Los compuestos de fórmula (I) de acuerdo a D2 no abarcan la estructura del tramadol. Además, D2 enseña claramente que los compuestos de fórmula (I) como (1R,2R)-3-(3-Dimetilamino-1-etil-2-metil-propil)-fenol no exhiben efectos secundarios como ocurre en algunos casos con el tratamiento con tramadol. Más aún, estos compuestos de fórmula (I) se distinguen por un marcado efecto analgésico, que es significativamente más intenso al compararlo con tramadol.

- Por lo tanto, el objetivo real de D2 no se refiere al tramadol, sino a mejorar el perfil de efectos secundarios y efecto analgésico comparado con tramadol al introducir un compuesto de fórmula (I) que difiere estructural y farmacológicamente del tramadol. Al respecto, un experto en el arte no habría tomado en consideración las enseñanzas de D1, el que trata únicamente de tramadol en combinación con acetaminofen, es decir, del compuesto cuyo perfil farmacológico se desea mejorar y del que no se hace referencia en D2.

- Debido a que los compuestos de fórmula (I) per se ejercen un efecto analgésico significativamente más intenso acompañado de menores efectos secundarios al compararlos con tramadol, una persona experta en la materia no estaría motivada a buscar un efecto sinérgico debido a que los compuestos de fórmula per se ejercen un alivio del dolor mejorado con menores efectos secundarios. Un experto en la materia no tendría incentivo especial a considerar las enseñanzas de D1 pues trata de tramadol, que es el compuesto que D2 no considera.

- A partir de D2 se hace evidente que los compuestos de fórmula (I) tales como (1R,2R)-3-(3-Dimetilamino-1-etil-2-metil-propil)-fenol ejercen un perfil farmacológico (farmacodinámico y farmacocinético) diferente al compararlo con el tramadol usado en la combinación de acuerdo a D1. Esto puede ser derivado fácilmente a

partir de lo divulgado en D2, en que los efectos analgésicos de los compuestos de fórmula general (I) son más pronunciados y con menores efectos secundarios comparados con el tramadol.

- Al respecto, se debe tener presente que el tramadol ejerce una única acción farmacológica que es diferente de aquella que ejercen los compuestos de fórmula (I) de acuerdo a D2 y, por lo tanto, difieren de los compuestos de la composición farmacológica de acuerdo a la presente invención.

- Para ilustrar los diferentes perfiles farmacológicos, farmacodinámicos y farmacocinéticos, se comparan tramadol y (1R,2R)-3-(3-Dimetilamino-1-etil-2-metil-propil)-fenol (indicado como tapentadol) de acuerdo a lo siguiente:

- El tapentadol de acuerdo a lo utilizado en la presente invención ejerce una actividad analgésica con un modo de acción dual: antagonismo del receptor μ -opioide (MOR) e inhibición de la recaptación de noradrenalina (NA). Además muestra mayor potencia al ser comparado con tramadol.
- La actividad del tapentadol reside en un único enantiómero y es independiente de la activación metabólica. No tiene metabolitos activos, y la principal vía metabólica para su eliminación es la glucurunidación fase II que es mediada por enzimas de la superfamilia UDP-glucuronosiltransferasa que resulta en la desactivación de la señal farmacológica. Las vías metabólicas fase I, que son mediadas, entre otros, por enzimas citocromo P-450, juegan un rol menor en la biotransformación de tapentadol y, por lo tanto, tienen bajo potencial para interacciones entre drogas, tal como se presenta en el trabajo de Tzschentke et al, incorporado como referencia. Otro artículo científico reciente que describe en detalle las diferencias funcionales y mecánicas de tapentadol y tramadol es el trabajo de Raffa et al. Que se acompaña también como referencia.
- En contraste, el tramadol ejerce su actividad analgésica a través del antagonismo con MOR, inhibición de la recaptación de NA e inhibición de la recaptación de serotonina (5-HT). El tramadol se usa como racemato con metabolitos activos, cada uno de los cuales tiene un perfil d actividad diferente. Por lo tanto, el tramadol muestra activación pro-droga. La inhibición de la recaptación de NA y 5-HT reside principalmente en los (-)-enantiómeros y (+)-enantiómeros de la composición madre de tramadol, respectivamente, mientras que la activación de

MOR reside en el (+)-enantiómero de O-desmetil-tramadol. El metabolito MOR-activo contribuye significativamente al perfil analgésico del tramadol. Ambos enantiómeros de tramadol y su metabolito O-desmetil son necesarios para el perfil analgésico del tramadol.

- Las vías metabólicas fase I juegan un rol importante en la biotransformación del tramadol, y por lo tanto pueden ser objeto de interacciones droga-droga relevantes (ver Tzschentke et al.).
- Al comparar la acción farmacológica de tapentadol con la de tramadol, es importante enfatizar que los diferentes mecanismos de acción de 1R,2R)-3-(3-Dimetilamino-1-etil-2-metil-propil)-fenol residen en la misma molécula, así la relación relativa de los mecanismos no cambia en el tiempo. En el caso del tramadol, sin embargo, los diferentes mecanismos de acción residen en diferentes moléculas (enantiómeros, metabolitos) y, por lo tanto, la contribución relativa de estos mecanismos cambia a medida que el tramadol se somete a biotransformación. Además, el tapentadol tiene un inicio de la acción más rápido comparado con el tramadol debido a que no es activado por enzimas metabólicas y cruza la barrera sangre-cerebro rápidamente.
- Como se muestra, el tapentadol y el tramadol muestran diferencias significativas en sus perfiles farmacodinámicos y farmacocinéticos. Por lo tanto, el tapentadol de acuerdo a como es usado en la composición de la presente invención, no es comparable con la acción farmacológica del tramadol, a pesar de que el examinador considere que ambos compuestos estén relacionados estructuralmente.
- Es así como un experto en la materia no habría estado motivado a combinar las enseñanzas de D1 y D2, y por tanto, la presente invención, además de tener novedad, cumple con tener actividad inventiva por sobre lo divulgado en el estado del arte. Por lo anteriormente expuesto consideramos que la presente solicitud es novedosa tiene nivel inventivo, las reivindicaciones definen la materia que se desea proteger siendo claras, concisas y debidamente sustentadas en la descripción y no está comprendida en el estado de la técnica, conforme lo establece el Art. 14, 16 y 30 de la Decisión 486.

De manera atenta solicito a su Despacho, tener en cuenta todos y cada una de las consideraciones expuestas anteriormente, al momento de estudiar el presente caso.

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Anexo:

- i. Nuevo capítulo reivindicatorio.
- ii. Nuevo capítulo descriptivo.
- iii. Documento Tzschentke et al
- iv. Documento Mechanistic and functional differentiation of tapentadol and tramadol
- v. Documento EP2012764

Petición:

Conforme a lo anterior, una vez atendidos los requerimientos y exigencias del examinador y al tener en cuenta los capítulos descriptivo y reivindicatorio modificados que se presentan con la presente contestación, solicito muy respetuosamente a su Despacho, continuar el trámite de rigor y de ser el caso se hagan las correspondientes observaciones con el ánimo de hacer lo pertinente dentro del presente trámite.

Atentamente,



HUMBERTO RUBIO CAMACHO

C.C. 17'192.062 de Bogotá

**T.P. 50.007 Consejo Superior
de la Judicatura**

COD. 4134

Combinación Farmacéutica que comprende 3-(3-dimetilamino-1 etil-2-metil-propil)-fenol y Paracetamol.

La presente invención se refiere a la combinación que comprende componentes
5 como (a) el compuesto (3-(3-dimetilamino-1etil-2-metil-propil)-fenol y (b) Paracetamol o derivados de él, una formulación farmacéutica y una dosis que comprende dicha combinación así como un método de tratamiento del dolor, e.g. dolor crónico o agudo caracterizado en esos componentes (a) y (b) son administrados simultáneamente o secuencialmente a un mamífero, donde el
10 componente (a) puede ser administrado antes o después que el componente (b) y donde los componentes (a) y (b) son administrados a un mamífero por la misma o diferente vía de administración.

El tratamiento de la condición de dolor crónico o agudo es extremadamente
15 importante en medicina. Existe actualmente una demanda mundial adicional, no exclusivamente, bases opioides, pero altamente efectivas en el tratamiento del dolor. La urgente necesidad de acción orientada a pacientes y un tratamiento útil a la condición de dolor, esto se está tomando para entender el éxito y satisfactoriamente el tratamiento del dolor para el paciente, está documentado
20 en un gran numero de papeles científicos que han aparecido recientemente en el campo de aplicación de analgésicos y un trabajo de investigación fundamental sobre nocicepción.

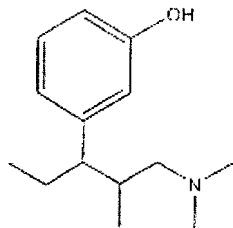
Incluso si los analgésicos que se usan actualmente para el tratamiento del dolor,
25 por ejemplo opioides, NA- e inhibidores 5HT-reabsorbidos, NSAIDS e inhibidores COX, son analgesicamente efectivos, sin embargo los efectos secundarios a veces ocurren. WO 204/047823 describen una combinación de sustancias que comprenden ciertos analgésicos, incluyendo compuestos 1-fenil-3-dimetilaminopropano e inhibidores COX-II, que muestra efectos súper-aditivos
30 sobre la administración. Debido al efecto súper-aditivo de la dosis total y en consecuencia del riesgo indeseado de efectos secundarios, se puede reducir.

Así, fue un objetivo de la presente invención encontrar más combinaciones que estén en acuerdo para el tratamiento del dolor y que preferiblemente una menor
35 exposición a los indeseados efectos secundarios comparado con los componentes individuales, si es administrado es dosis efectiva.

Ha sido encontrado que una combinación que comprende (a) el compuesto 3-(3-Dimetilamino-1-etil-2-metil-propil)-fenol y (b) Paracetamol o derivados de ellos exhiben un efecto analgésico. Si estos componentes están presentes en la composición, en una proporción tal de peso que un efecto sinérgico es observado después de la administración al paciente, la total administración de la dosis puede bajar, a fin de bajar el efecto secundario indeseado que puede ocurrir.

En consecuencia, la presente invención se refiere a una combinación farmacéutica que comprende como componentes

(a) 3-(3-Dimetilamino-1-etil-2-metil-propil)-fenol de fórmula (1)



(I).

Opcionalmente en forma de uno de estos estero isómeros puros, en particular un enantiomero o un diastereoisomero, en racimato o en forma de mezcla de estero isómeros, en enantiomeros particulares y/o diastomeros en cualquier proporción de mezcla o cualquier adición de sal de acido correspondiente a ello o cualquier solvente de ello y

(b) Paracetamol o derivado del mismo

En un entorno de combinación inactiva el componente (a) se selecciona de

(1R, 2R)- 3-(3-Dimetilamino-1-etil-2-metil-propil)-fenol,
 (1S, 2S)- 3-(3-Dimetilamino-1-etil-2-metil-propil)-fenol,
 (1R, 2S)- 3-(3-Dimetilamino-1-etil-2-metil-propil)-fenol,
 (1S, 2R)- 3-(3-Dimetilamino-1-etil-2-metil-propil)-fenol y cualquier mezcla del mismo

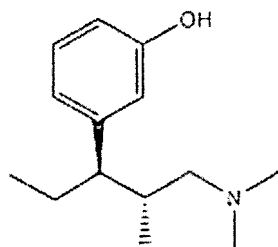
En otro entorno de combinación inactiva el componente (a) se selecciona

(1R, 2R)- 3-(3-Dimetilamino-1-etil-2-metil-propil)-fenol y

(1S, 2S)- 3-(3-Dimetilamino-1-etil-2-metil-propil)-fenol y cualquier mezcla del mismo

Aún otro entorno de combinación inactiva comprende

(a) El componente (1R, 2R)- 3-(3-Dimetilamino-1-etil-2-metil-propil)-fenol, de la formula (I')



(I')

O una adición de sal de ácido de ello y

(b) Paracetamol o derivado del mismo

El componente 3-(3-Dimetilamino-1-etil-2-metil-propil)-fenol de formula (I), su estero isómero y correspondiente sal del mismo así como métodos para su preparación son bien conocidos por ejemplo US 6,248,737 B1. La parte respectiva de la descripción quedan incorporadas por referencia y forman parte de la presente divulgación.

La definición del componente (a) como se usa aquí incluye al compuesto 3-(3-Dimetilamino-1-etil-2-metil-propil)-fenol y sus estero isómeros en cualquier forma posible, por lo tanto, particularmente incluye solventes, adición de sal de ácido y solventes correspondientes y polimorfos de ello.

Si el componente (a) está presente como mezcla de enantiómeros, tal mezcla puede contener los enantiómeros en forma de racimo o no-racimo. La forma de

no-racimo puede por ejemplo contener los enantimeros en una proporción de 60:40,70:30,80:20 ó 90:10.

- El compuesto 3-(3-Dimetilamino-1-etil-2-metil-propil)-fenol y sus estero isómeros
- 5 en acuerdo con el componente (a) puede estar presente en la composición inventiva farmacéutica en forma de una adicción de sal de acido, según el cual cualquier acido apropiado capaz de formar sólo una adicción de sal puede ser usado.
- 10 La conversión del compuesto 3-(3-Dimetilamino-1-etil-2-metil-propil)-fenol en una correspondiente adicción de sal mediante reacción con un acido apropiado puede ser efectuada de la manera que saben los expertos en la materia. Ácidos apropiados se incluyen, pero no están limitados a acido hidrociorhidrico, acido hidrobromico, acido sulfúrico, acido metano sulfúrico, acido formico, acido
- 15 acético, acido oxálico, acido succínico, acido tartarico, acido madelico, acido fumarico, acido láctico. Acido cítrico, acido glutámico y/o acido aspartico. La formación de sal es preferiblemente efectuada en un solvente, por ejemplo dietil eter, dosopropil eter, alquil acetato, acetona y/o 2-butanona, Má aún, trimetilclorosilano en solución acuosa es también apropiado para la preparación
- 20 de hidrociorhidricos.

- Es sabido para aquellos expertos en la materia que la acción analgésica de los las drogas antiinflamatorias no-esteroidales (NSAIDs) es debido a la inhibición de la producción enzimático en la conversión de acido araquidónico derivado de
- 25 lípidos de la membrana celular de las prostaglandinas y otros eicosanoides. COX existe en dos isoformas diferentes caracterizadas por diferentes expresiones de patrones. COX-I es constitutivamente expresado en muchas células del cuerpo y principalmente responsable para la producción de eicosanoides al servicio de las funciones fisiológicas normales. La expresión COX- II es inducida durante la
- 30 inflamación y también COX-II se expresa en el sistema nervioso central.

Paracetamol y sus derivados no muestra ninguna actividad antiinflamatoria significativa y por lo tanto no son considerados para ser NSAIDs.

El termino paracetamol, es también conocido como acetaminofen y sus derivados, tal como se utilizan en este documento incluyen estos componentes en cualquier forma posible, así incluye solventes y polimorfos de ello.

- 5 El termino derivado como es usado en este documento particularmente incluye pro-drogas, tales como éteres y esteres de Paracetamol. métodos apropiados para seleccionar y preparar pro-drogas de una sustancia dada son por ejemplo descritas en "Textbook of Drug Desing and Discovery", 3ra edition, 2002, capitulo 14, paginas 410-458, Editores: Krogsgaard - Laser et al, Taylor y
- 10 Francis. Las respectivas partes de dicha descripción literaria es incorporada como referencia y forma parte de la presente divulgación.

- Paracetamol y sus derivados así como Paracetamol y Penidina así como los procesos para su preparación son bien conocidos en la materia por ejemplo de
- 15 E. Friderichs et al, "Analgesics and Antipyretics", Ullmann`s of Industrial Chemistry, sexta edición, Wlley-VCH Verlag GMBH, Alemania 2000, paginas 1-22 y H.Buschmann, T. Christoph, E. Friderichs, C. Maul, B. Sundermann, "Analgesics From Chemistry and Pharmacology to Clinical Application", 2002, Parte II, Wlley-VCH Verlag, Alemania. Las respectivas partes de dicha
- 20 descripción literaria es incorporada como referencia y forma parte de la presente divulgación.

- En un entorno de combinación inventiva el derivado del Paracetamol en acuerdo con el componente (b) es seleccionado de un grupo conformado por el Pro
- 25 paracetamol y Penidina.

En un entorno específico de la presente invención es la combinación que comprende

- 30 (a) (1 R, 2R)-3-(3-Dimetilamino-1-etil-2-metil-propil)-fenol o el hidroclohidrico además la adición de sal del mismo y (b) Paracetamol

- Ambos componentes (a) y (b) como parte de la combinación inventiva puede ser administrada en su dosis diaria. La dosis diaria de paracetamol, preferiblemente
- 35 no debería exceder 4g para adultos. Para lactantes y niños la dosis diaria, preferiblemente no debería exceder 90 mg/kg. Preferiblemente el compuesto (1

R, 2R)-3-(3-Dimetilamino-1-etil-2-metil-propil)-fenol puede ser administrado a un paciente en dosis diaria de 25 a 1000 mg., particularmente preferible en una dosis de 50 a 800 mg más particularmente preferible en una dosis de 100 a 600 mg.

5

En otro entorno de la presente invención la combinación puede contener componentes (a) y (b) esencialmente en una proporción equiefectiva.

Aún en un nuevo entorno de la combinación inventiva de componentes (a) y (b) están presentes en una proporción de peso que la composición resultante podrá ejercer un efecto sinérgico sobre la administración al paciente. Una proporción de peso apropiada puede ser determinada por métodos bien conocidos por los expertos en la materia, e.g. mediante el test Randall-Selitto, descrito más abajo.

15 Ambos componentes (a) y (b) también pueden ser presentados en la combinación inventiva en proporciones desviadas de la proporción equiefectiva, Por ejemplo cada componente puede ser presentado en un rango de 1/5 de cantidad equiefectiva a 5 veces de cantidad equiefectiva, preferiblemente 1/4 a 4, más preferiblemente 1/3 a 3, aún más preferiblemente 1/2 a 2 de la cantidad equiefectiva.

En otro entorno de la presente invención los componentes (a) y (b) pueden ser administrados en un régimen de dosis específica para tratar al dolor, por ejemplo dolor crónico o dolor agudo. Componentes (a) y (b) pueden ser administrados simultáneamente o secuencialmente una de la otra, en cada caso por vía de la misma o de diferentes vías administración. Otro aspecto de la presente invención es, por lo tanto, un método para tratar el dolor, e. g., dolor crónico o agudo, caracterizados en esos componentes (a) y (b) son administrados simultáneamente o secuencialmente a un mamífero, donde los componentes (a) o (b) son administrados a un mamífero ya sea la misma vía o por diferentes vías de administración. Las vías adecuadas de administración incluidas, pero no limitadas a administración oral, intravenosas, intraperitoneal, transdermica, intratraqueal, intramuscular, intranasal, transmucosal, subcutanea o rectal.

30

Las combinaciones inventivas son toxicológicamente seguras y son, por lo tanto, adecuadas para el tratamiento de mamíferos, particularmente humanos incluyendo lactantes, niños y adultos.

- 5 Así, en un nuevo aspecto la presente invención se refiere a una composición farmacéutica que comprende una composición inventiva como es descrita en este documento y uno o más agentes auxiliares.

- En un nuevo aspecto la presente invención se refiere a una dosis farmacéutica
10 que comprende una composición inventiva como es descrita en este documento y uno o más agentes auxiliares.

- En un entorno, la forma de dosificación farmacéutica inventiva es adecuada para ser administrada oralmente, intravenosamente, itraperitonealmente,
15 intratraquealmente, intramuscularmente, intranasalmente, transmucosalmente, subcutáneamente o rectalmente.

- Las formulaciones inventivas y la forma de dosificación puede contener agentes auxiliares por ejemplo, transportadores, rellenos, solventes, diluyentes,
20 colorantes y/o aglutinantes. La selección de agentes auxiliares y la cantidad de ellos que serán usados depende por ejemplo, de la forma en que la droga será administrada, e. g., oralmente, intravenosamente, itraperitonealmente, intratradermicamente, intramuscularmente, intranasalmente o localmente, por ejemplo, para infecciones de la piel, de las membranas mucosas o de los ojos.

25

Agentes auxiliares adecuados en el contexto de esta invención son cualquier sustancia conocida por una persona experta en la materia, útiles para la preparación de formulaciones galénicas.

- Ejemplos de agentes auxiliares adecuados incluyen, pero no se limitan a agua,
30 etanol, propanol, glicerol, etileno glicol, fructosa, lactosa, sacarosa, dextrosa, melasa, almidón, almidón modificado, gelatina, sorbitol, inositol, manitol, celulosa microcristalina, metil celulosa, carboximetil celulosa, celulosa acetato, shellac, cetil alcohol, polivinil pirrolidone, parafinas, ceras, gomas naturales y sintéticas, goma acacia, alginatos, dextran, ácidos grasos saturados e insaturados, ácido
35 esteárico, magnesio esterato, zinc esterato, sodio lauril sulfato, aceites comestibles, aceite de sésamo, aceite de coco, aceite de maní, aceite de soya,

- lecitina, sodio lactato, polioxietileno y polipropileno de esteres de ácidos grasos, sorbitano de esteres de ácidos grasos, ácido sórbico, ácido benzoico, ácido cítrico, ácido sórbico, ácido tánico, cloruro de sodio, cloruro de potasio, cloruro de magnesio, cloruro de calcio, óxido de magnesio, óxido de zinc, dióxido de
- 5 silicona, óxido de titanio, dióxido de titanio, sulfato de magnesio, sulfato de zinc, sulfato de calcio, potasa, fosfato de calcio, fosfato de dicalcio, bromuro de potasio, yoduro de potasio, talco, caolina, pectina, crosspovidona, agar y bentonita.
- 10 Formulaciones farmacéuticas (formas de dosificación) en la forma de tabletas, tabletas efervescentes, tabletas masticables, dulces, capsulas, gotas, pellets, esferas, cristales y los mismos opcionalmente comprimidos en una tableta, aglutinados en una capsula, aglutinados en un sachet o suspendidos en un medio líquido adecuado, Formulaciones farmacéuticas orales pueden también
- 15 estar recubiertas con una cubierta entérica.

Formulaciones farmacéuticas que son adecuadas para administración parenteral, tópica e inhalativa, incluyen, pero no se limitan a soluciones, suspensiones, preparaciones secas de fácil reconstitución y spray.

20

Supositorios son formulaciones farmacéuticas adecuadas para la administración rectal. Formulaciones en un depósito, en forma disuelta, por ejemplo, en un parche opcionalmente con la adición de un agente que promueve la penetración en la piel, son ejemplos de formulaciones para la administración percutánea.

25

Uno o ambos componentes (a) y (b) pueden estar presente en la fórmula farmacéutica inventiva al menos parcialmente en la forma de liberación controlada.

- Más aún, cualquier combinación de liberación controlada/liberación inmediata de
- 30 dichos componentes también pueden estar presente en la formulación farmacéutica inventiva. Por ejemplo, uno o ambos componentes puede ser liberado de la formulación inventiva con cierta demora, e. g., si son administrados oralmente, rectalmente o percutáneamente. Tales formulaciones son particularmente útiles para preparaciones "una vez al día" o "dos veces al
- 35 día", que sólo deben ser tomadas una vez al día, respectivamente, dos veces al día.

Materiales adecuados para una liberación controlada son bien sabidos por una persona experta en la materia.

- La formulación farmacéutica inventiva puede ser producida usando materiales, medios, dispositivos y procesos que son bien conocidos en la técnica de formulaciones farmacéuticas, como se describen por ejemplo en "Remington's Pharmaceutical Sciences" A.R. Gennaro (ed.), 17a edición, Marck Publishing Company, Easton Pa. (1985), en particular en la parte 8, capítulos 76 al 93.
- En orden de obtener una formulación farmacéutica sólida, tal como una tableta por ejemplo los componentes de la composición farmacéutica pueden ser granulados con un transportador farmacéutico, por ejemplo ingredientes convencionales para tabletas tales como almidón de maíz, lactosa, sacarosa, sorbitol, talco, magnesio estearato, fosfato de calcio o gomas farmacéuticamente aceptables y diluyentes farmacéuticos por ejemplo agua, en el orden de formar una composición sólida que contenga a los componentes en una distribución homogénea. El término "distribución homogénea" es tomado en el sentido de que los componentes son distribuidos uniformemente sobre la composición total, por lo que dicha composición pueda ser fácilmente divisible en equitativamente en la forma de dosis unitaria efectiva, tales como, tabletas, píldoras o capsulas. La composición sólida es luego dividida en forma de dosis unitaria. Las tabletas o píldoras de la composición farmacéutica en acuerdo con la invención pueden también ser recubiertas o compuestas en una manera diferente, en el orden de proveer una forma de dosis con una liberación controlada.
- Si uno de los componentes, e.g. componente (b), va a ser liberado previamente al otro componente, por ejemplo al menos 30 minutos o 1 hora, de antelación, formulaciones farmacéuticas pueden ser preparadas teniendo una curva de liberación correspondiente. Un ejemplo de dicha formulación es un sistema de liberación impulsada osmoticamente para lograr un retaso en la liberación del componente (a) mediante el recubrimiento que contiene en sí al componente (b) que fue en consecuencia liberado antes. En un sistema de liberación de este tipo, que es particularmente aceptable para una administración oral, al menos parte y preferiblemente toda la superficie del sistema de liberación, preferiblemente aquellas partes que tomaran contacto con el medio de liberación es/son semipermeables, preferiblemente equipada con cobertura semipermeable

por lo que la superficie(s) es/son permeables al medio de liberación, pero sustancialmente, preferiblemente totalmente impermeable para ingredientes activos, componente (a) la superficie(s) y/o opcionalmente la cobertura abarca al menos una abertura para la liberación del ingrediente activo, Componente (a).

- 5 Más aún precisamente esa/esas superficie(s) que está/están en contacto con el medio de liberación es/son provistas con una cobertura que contiene y libera al otro componente, componente (b). Esto es preferiblemente en el sentido de un sistema en forma de tableta que abarque una liberación abierta, un núcleo osmótico de composición farmacéutica, una membrana semipermeable y una
- 10 porción de polímero que ejerza presión sobre la hinchazón. Un ejemplo adecuado para este tipo de sistemas, es el sistema distribuido por ALZA Corporation, USA bajo la marca registrada ORO®, en particular, OROS® el Sistema Push-Pull TM, OROS® el Sistema Multi-Capa Push-Pull TM, OROS® Sistema Push-Stick y también, en cajas específicas de L-OROS TM.

15

Entornos y ejemplos del sistema de liberación impulsada osmoticamente, son por ejemplo divulgadas en las patentes de EEUU 4.765.989, 4.783,337, todo el contenido respectivo de los cuales se incorporan por referencia y forma parte de la divulgación de la presente invención.

20

Un ejemplo más adecuado para formulación farmacéutica es una tableta de gel de matriz, así como los productos desarrollados por Penwest Pharmaceuticals (por ejemplo, bajo tiempoRX). Ejemplos adecuados son provistos en patentes de EEUU 5.330.761, 5.399.362, 5.472.711 Y 5.455.046 todo el contenido respectivo

- 25 de los cuales se incorporan por referencia y forma parte de la divulgación de la presente invención.

Particularmente adecuada es el retardo de la formulación de matriz, con distribución inhomogenea de la composición farmacéuticamente activa, que por ejemplo el componente (b) puede ser distribuido en la región exterior (la porción

30 que se pone en contacto con el medio de liberación más rápido) de la matriz y de otro componente (a) es distribuido dentro de la matriz. En contacto con el medio de liberación, la capa exterior de la matriz inicialmente (y rápidamente) se hincha y primeramente libera al componente Paracetamol, seguido por la significativa mente (más) retardada liberación del componente (a).

- 35 Ejemplos de una matriz adecuada incluye matrices de un 1 a un 80% por peso de uno o más polímeros higofilicos o hidrofobicos como formadores de matriz

farmacéuticamente aceptable. Además un ejemplo adecuado de matriz se puede deducir de las patentes de EEUU 4.389.393, todo el contenido respectivo de los cuales se incorporan por referencia y forma parte de la divulgación de la presente invención.

5

La cantidad de la combinación inventiva farmacéuticamente activa podrá ser administrada a pacientes, puede variar dependiendo de diferentes factores bien conocidos por aquellos expertos en la materia, por ejemplo, el peso del paciente, la ruta de administración o la severidad de la enfermedad.

10

En un nuevo aspecto la presente invención se refiere al uso de una combinación inventiva como se describe en este documento, para la preparación de un medicamento para el tratamiento del dolor.

15 En otro entorno la presente invención se refiere al uso de una combinación inventiva como se describe en este documento, para la preparación de un medicamento para el tratamiento del dolor, donde el dolor es seleccionado desde dolor inflamatorio, dolor neuropático, dolor agudo, dolor crónico, dolor visceral, dolor de migraña y dolor del cáncer.

20

Aún en otro aspecto de la presente invención se refiere a un método de tratamiento del dolor en mamíferos, preferiblemente humano, que abarca administrar una cantidad efectiva de una combinación inventiva como se describe en este documento al mamífero.

25

En un nuevo aspecto de la presente invención se refiere a un método de tratamiento del dolor en mamíferos, preferiblemente humano, que abarca administrar una cantidad efectiva de una combinación inventiva como se describe en este documento al mamífero, donde el dolor es seleccionado desde

30 dolor inflamatorio, dolor neuropático, dolor agudo, dolor crónico, dolor visceral, dolor de migraña y dolor del cáncer.

métodos Farmacológicos:

35 A. Randall-Selitto prueba en ratas

Las proporciones de peso de los componentes (a) y (b) que dará lugar a un efecto súper-aditivo (efecto sinérgico) de la composición inventiva farmacéutica puede ser determinada mediante la prueba de Randall y Selitto, como se describe en Arch. Int. Pharmacodyn., 1957, 111:409 a 419, donde es un modelo para el dolor inflamatorio. La parte respectiva de la literatura es incorporada a este documento por la referencia y forma parte de la presente divulgación.

Por medio de inyección de 0.1 ml de suspensión de Carregenina ventralmente en la pata posterior de una rata, un edema es inducido en donde el dolor es generado 4 horas después continuamente por un aumento de presión, con un sello (2mm de diámetro de la punta). La actividad antinociceptiva y antihiperálgica de la sustancia de prueba es determinada en diferentes puntos en un tiempo después de la administración de la sustancia. El valor que se determine y, al mismo tiempo también el punto final de la prueba del dolor es la presión a la que la reacción de vocalización ocurre en la rata. El máximo porcentaje de efecto posible (%MPE) es calculado. La máxima presión del sello es 250 g. El tamaño del grupo es n=10.

El análisis de los resultados con respecto a efecto súper-aditivo de la composición inventiva farmacéutica abarca los componentes (a) y (b) es llevada a cabo mediante una comparación estática de un aditivo teórico valor – ED₅₀ es experimentalmente, valor - ED₅₀ de una llamada combinación de proporción fija (isobolographic analysis en acuerdo con Tallarida JT, Porreca F, and Cowan A. Statical análisis of drug-drug and site-site interactions with isobolograms. Life Sci 1989;45:947-961).

La interacción de estudios presentados en este documento fueron realizados usando dosis efectivas de los dos componentes, calculadas por la proporción del
 5 respectivo valores -ED₅₀ de los componentes administrados solos.

La ruta de aplicación fue intravenosa (i.v.) para (1R, 2R)-3-(3-Dimetilamino-1-etil-2-metil-propil)-fenol (A) e intraperitoneal (i.p.) para Paracetamol. Cuando A fue aplicado solo, el máximo efecto fue registrado a los 15 min. p. appl. (punto de
 10 tiempo de la primera medida) y un valor -ED₅₀ de 1.878 (1.694-2.065)mg/kg i.v fue calculado.

Paracetamol inducida por una dosis-dependiente del efecto analgésico con un valor - ED₅₀ de 189,9 (181,3 - 198,4) mg/kg i.p. respectivamente alcanzando el máximo efecto 120 min. P. appl.

15 En acuerdo con sus respectivos puntos de tiempo del máximo efecto (1R, 2R)-3(3-Dimetilamino-1-etil-2-metil-propil)-fenol fue aplicado a los 15 min. y Paracetamol 120 min. antes el punto de tiempo de la medida de la interacción de los experimentos (i.e. Paracetamol fue aplicado 105 min. antes (1R, 2R)-3-(3-Dimetilamino-1-etil-2-metil-propil)-fenol respectivamente). Así el punto de tiempo
 20 de ED₅₀ el cálculo de la combinación corresponde al punto de tiempo del máximo efecto del respectivo componente. Los análisis isobolograficos revelan que los valores - ED₅₀ experimentales de las combinaciones fueron significativamente menores que los respectivos valores - ED₅₀ teóricos. Así, estudios combinados demuestran una interacción sinérgica significativa de
 25 (1R, 2R)-3-(3Dimetilamino-1-etil-2-metil-propil)-fenol con Paracetamol.

Los resultados de los análisis isobolograficos están resumidos en la siguiente tabla.

30 Valores - ED₅₀ experimentales y Paracetamol y análisis isobolografico de la interacción entre A y paracetamol:

	A	Para- cetamol	ED50 Teórico de la combinación de A y Paracetamol	ED50 Experimental de la combinación de A y Paracetamol	Interacción
Sustancia ED50 (mg/kg) (intervalo de confianza)	1,878 (1,694- 2,065)*	189,9 (181,3- 198,4)	95,90(90,75- 101,0)	74,88(66,63- 84,17)	Súper- aditivo (p 0,001)

p: Nivel de estática significativo

De la tabla 1 dada arriba, la proporción de A a Paracetamol podrá calcularse a ser 1 : 101

El siguiente ejemplo intenta aclarar la invención restringir el objetivo de la invención a dicho ejemplo.

10 Ejemplo:

Preparación de una tableta de Paracetamol combinada

Composición

- 15
- Paracetamol

5000 g
- (1 R, 2R)-3-(3-Dimetilamino-1-etil-2-metil-propil)-fenol

500 g
- Povidona K25

100g
- Celulosa Microcristalina

300g
- 20

Celulosa en Polvo

140g

Acido esteárico

60g

Povidona es disuelta en 1.5 litros de agua. Paracetamol y (1R, 2R)-3-(3-Dimetilamino-1-etil-2-metil-propil)-fenol son mezclados en un mezclador de alta cizalla y los compuestos son granulados por la adicción de una solución de povidona. El tamaño de la masa húmeda pasa por un tamiz de 3 mm y es
5 secado en un horno a 50°C. La masa seca junto con la celulosa microcristalina y polvo de celulosa pasa por un tamiz de 1 mm. La masa es mezclada junto con ácido esteárico que pasó por un tamiz de 0.315 mm. La masa final es prensada en una tableta Korsch EK10, prensada en tabletas de 13 mm de diámetro y un peso de 610 mg cada una.

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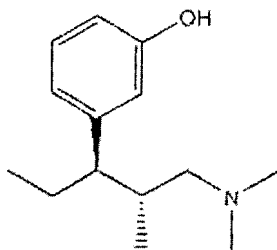
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Reivindicaciones

- 5 1. Composición farmacéutica CARACTERIZADA porque abarca como componentes:

a) un compuesto (1R, 2R)-3-(3-Dimetilamino-1-etil-2-metil-propil)-fenol de la formula (I')

10



15

(I')

o una adición de sal de ácido de ello, donde en la adición de sal de ácido se prefiere el hidrocloreuro; y

(b) paracetamol.

- 20 2. Composición farmacéutica de acuerdo con la reivindicación 1, CARACTERIZADA porque los componentes (a) y (b) están presente en tal proporción de peso donde la composición puede ejercer un efecto sinérgico sobre la administración a un paciente.

- 25 3. Composición farmacéutica de acuerdo con la reivindicación 1, CARACTERIZADA porque además abarca uno o más agentes auxiliares.

30

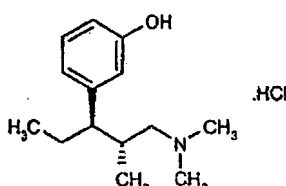
Tapentadol Hydrochloride

Prop INNM, USAN

*Analgesic
Mu-Opioid Receptor Agonist
Noradrenaline Reuptake Inhibitor*

CG5503
BN200

(-)-(1*R*,2*R*)-3-(3-Dimethylamino-1-ethyl-2-methylpropyl)phenol hydrochloride



C₁₄H₂₃NO.HCl

Mol wt: 257.80

CAS: 175591-09-0

CAS: 175591-23-8 (as free base)

EN: 232967

Abstract

Tapentadol is a novel, investigational, centrally acting analgesic with a dual mode of action: mu-opioid receptor agonism and noradrenaline reuptake inhibition. Tapentadol showed analgesic effects in a wide range of animal models of acute, inflammatory and chronic neuropathic pain. Both mechanisms of action were shown to contribute to its analgesic effects. Generally, the potency of tapentadol was between that of morphine and tramadol. The activity of tapentadol resides in a single enantiomer and is independent of metabolic activation. It has no active metabolites, and the main metabolic pathway for elimination of tapentadol is phase II glucuronidation. Thus, tapentadol has a low potential for drug-drug interactions. Preclinical studies suggest a favorable tolerability profile compared to pure mu-agonists. Data from early clinical studies suggest improved gastrointestinal tolerability compared to morphine at doses producing similar efficacy. Phase III clinical trials are currently investigating the therapeutic potential of this innovative compound.

Synthesis

Tapentadol hydrochloride is synthesized by ether cleavage (e.g., conc. HBr) from its corresponding methyl ether (III). Compound (III) can be obtained by several

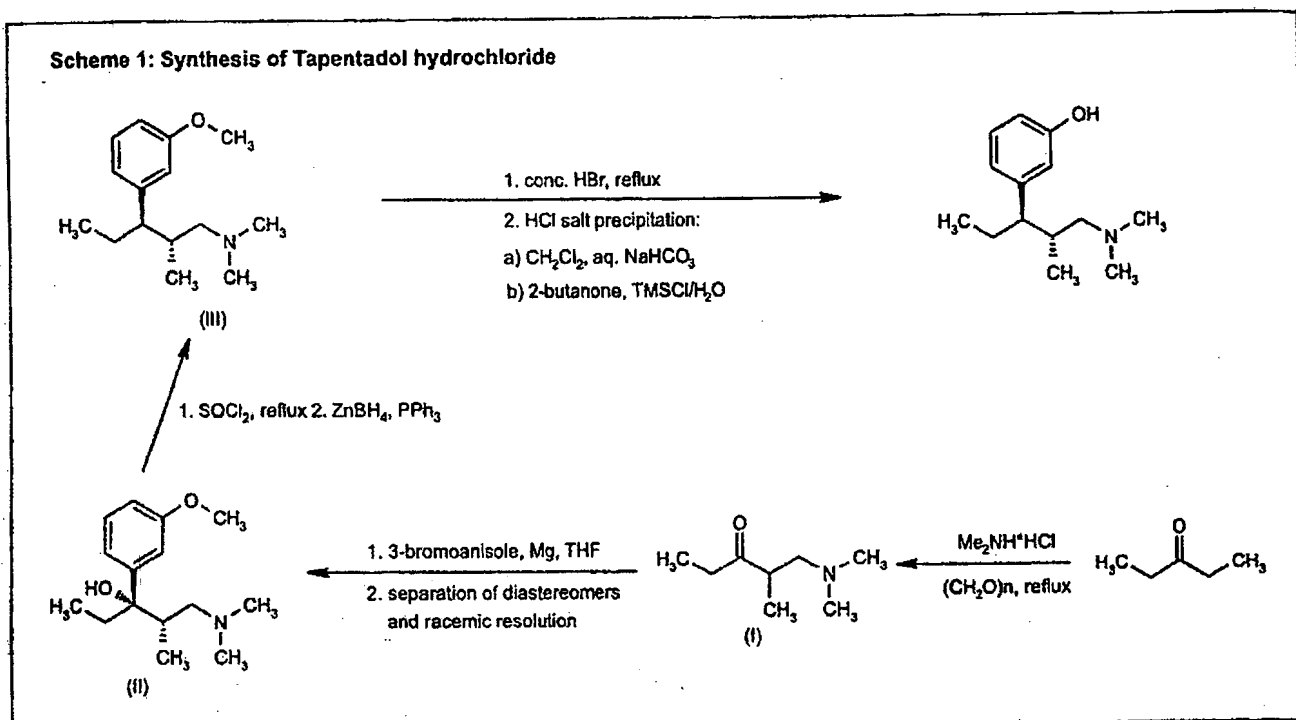
methods, e.g., starting from diethyl ketone, which is transformed under standard Mannich conditions to racemic (I). The Grignard reaction with 3-bromoanisole and subsequent separation of diastereomers (crystallization as HCl salt from 2-butanone with TMSCl/H₂O) and enantiomers (HPLC, CS phase) gives (-)-(S,S)-(II). Removal of the hydroxy group can be achieved diastereoselectively (under retention) by chlorination with thionyl chloride, followed by treatment with zinc borohydride (from ZnCl₂ and NaBH₄), leading to (-)-(R,R)-(III) (Scheme 1).

Background

Compounds that activate opioid receptors, in particular the mu-opioid receptor (MOR) subtype, have been used for many decades for the treatment of moderate to severe pain (1). However, extensive clinical experience with the prototypical MOR agonist morphine indicates that, although this compound is very effective against acute pain, it may be less effective against chronic pain conditions, especially those of neuropathic or inflammatory origin (2, 3). The finding that chronic pain can lead to MOR downregulation may offer a molecular basis for the relative lack of efficacy of morphine in long-term treatment settings (4). Moreover, prolonged treatment with morphine may result in tolerance to its analgesic effects, most likely due to treatment-induced MOR downregulation and other regulatory mechanisms. As a consequence, long-term treatment can result in substantial increases in dosing in order to maintain a clinically satisfactory analgesic effect. Furthermore, morphine has a limited therapeutic window, as its analgesic efficacy generally coincides with diverse side effects. These side effects are dose-limiting and result in poor patient compliance, especially in the case of chronic pain (5, 6). Nausea and emesis are typical for classical MOR agonists and

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Scheme 1: Synthesis of Tapentadol hydrochloride



appear directly after the start of treatment. Nausea and emesis are normally transient in the first week of treatment, but have a negative impact on patient compliance in this early treatment phase. Further side effects typical of morphine and other MOR agonists are constipation, mental clouding and respiratory depression, the latter being a rare but life-threatening event. Moreover, prolonged use of opioids results in physical dependence and may lead to addiction. Taken together, these points indicate that there is a significant medical need for safer and more tolerable opioids with an improved efficacy profile in chronic pain therapy.

Since the isolation of morphine two centuries ago, numerous derivatives have been synthesized, with the primary aim of separating analgesic effects from unwanted effects (7-9). However, the cloning of the MOR and the use of transgenic mice lacking this receptor (10, 11) indicated quite convincingly that both the analgesic efficacy and the unwanted effects of morphine and its analogues are mediated by the same receptor (*i.e.*, the MOR). This strongly suggests that a dissociation of analgesia from these unwanted effects can not be achieved with a selective MOR agonist.

An alternative approach to improve the therapeutic usefulness of opioid analgesics is to combine MOR activation with an additional mechanism of action aimed at enhancing analgesic efficacy. Such an additional analgesic mechanism may result in an opiate-sparing effect, thereby attenuating the unwanted effects of MOR activation. Activation of the noradrenergic descending pain-inhibitory pathway can be considered a candidate for such an additional mechanism. Compounds that inhibit the reuptake of noradrenaline (NA) are effective analgesics, particularly against chronic pain conditions in

which opioids are considered to be less effective or problematic due to their side effects (12-15). This mode of action was shown to be particularly effective in neuropathic pain (16). It was also demonstrated that such compounds can potentiate the analgesic effects of morphine (17, 18).

The concept of combined mechanisms of action was realized for the first time with the introduction of tramadol, a compound that produces MOR activation and inhibition of serotonin (5-HT) and NA reuptake (19-21). Tramadol is a racemate with active metabolites (22), each of which has a different profile of activity. NA and 5-HT reuptake inhibition mainly reside in the (-) and (+) enantiomer of the parent compound, respectively, whereas MOR activation resides in the (+) enantiomer of O-desmethyl-tramadol, and to a lesser degree in (+)-tramadol itself (23). Interestingly, it was shown that systemic administration of either (-) or (+)-tramadol in humans induces analgesia (24, 25), leading to the suggestion that a noradrenergic mechanism may contribute to the analgesic profile of racemic tramadol. In addition, it was found that the analgesic efficacy of tramadol was less pronounced in subjects who showed a reduced capability to form the (+)-O-desmethyl metabolite ("poor metabolizers"), as compared to subjects who produced relatively high levels of the metabolite. This indicates that the MOR-active metabolite contributes significantly to the analgesic profile of tramadol (26). Therefore, it was postulated that both enantiomers and the O-desmethyl metabolite are necessary for the full analgesic profile of tramadol (27, 28).

It can be argued, however, that inhibition of 5-HT reuptake contributes less to the analgesic profile of tramadol than MOR activation and NA reuptake inhibition.

First, it is highly likely that the analgesic efficacy of (+)-tramadol is (at least in large part) mediated by the (+)-O-desmethyl metabolite, which relatively potently activates the MOR. Second, and more importantly, it was found that while tramadol-induced analgesia is partially blocked by co-administration with either the MOR antagonist naloxone or the NA receptor antagonist yohimbine, it was completely abolished by combined administration of both antagonists (26). Also, preclinical and clinical evidence with selective 5-HT reuptake inhibitors, selective NA reuptake inhibitors and mixed 5-HT/NA reuptake inhibitors indicates that analgesia is more readily obtained by NA reuptake inhibition than by 5-HT reuptake inhibition (14, 16, 29, 30).

Therefore, it appears that the combination of MOR activation with NA reuptake inhibition should provide an improved and potent analgesic with high efficacy against acute and chronic pain conditions and an improved side effect profile compared to classical MOR agonists. In order to establish this novel pharmacological concept, an extensive synthesis program was initiated at Grünenthal, with the aim of combining MOR activation and NA reuptake inhibition in one chemical entity (i.e., "dual mode of action" concept).

The present paper reviews the preclinical and early clinical profile of tapentadol, one of the molecules resulting from this program that combines the dual mode of action in a single chemical entity, without active metabolites. The compound shows a broad analgesic profile in animal models of acute and chronic pain. In addition, it has a lower propensity to produce tolerance and physical dependence, and it may have an improved therapeutic window compared to morphine.

Preclinical Pharmacology

Tapentadol was characterized as a MOR agonist and NA reuptake inhibitor. The compound showed K_i values

of 0.1 and 0.5 μM in a rat MOR binding assay and a rat synaptosomal NA reuptake assay, respectively. Affinity for the other opioid receptor subtypes (i.e., kappa-opioid receptor [KOR], delta-opioid receptor [DOR] and ORL1 receptor [NOP]) was at least approximately 1 order of magnitude lower (Table I). The affinity of morphine at the MOR was about 50-fold higher than that of tapentadol. At the recombinant human MOR, both tapentadol and morphine had a somewhat lower affinity than at the rat MOR ($K_i = 0.54$ and $0.023 \mu\text{M}$, respectively).

Tapentadol was characterized in a GTP γS assay with human recombinant MOR as a MOR agonist ($\text{EC}_{50} = 0.67 \mu\text{M}$). MOR agonism was confirmed in a guinea pig ileum assay. In this test, electrically induced twitch contractions of the ileum were inhibited with an IC_{50} value of $1.49 \mu\text{M}$, an effect that was antagonized by the MOR antagonist naloxone.

In addition to its MOR-agonist effect, tapentadol was found to inhibit the reuptake of NA, as assessed in isolated rat brain synaptosomes, with a K_i value of $0.5 \mu\text{M}$. In contrast to its NA reuptake-inhibitory properties, the reuptake of 5-HT was only weakly inhibited ($K_i = 2.4 \mu\text{M}$) and dopamine and choline uptake was not affected to any relevant degree (Table II). To ascertain that the results measured in the synaptosomal uptake assay represented the appropriate neurotransmitter reuptake systems, binding assays with rat and human transporters were also performed. The results of these assays confirmed the data obtained with the functional reuptake systems.

Further assessment of the target selectivity of tapentadol was performed in a screening profile including more than 50 neurotransmitter receptors, reuptake transporters, ion channels and enzyme systems, including cyclooxygenases. These studies indicated that tapentadol showed submicromolar affinity for muscarinic M_1 - M_5 receptors ($K_i = 0.47$ - $1.19 \mu\text{M}$). Interaction with the muscarinic receptor was further assessed in the acetylcholine-induced guinea pig ileum contraction assay. The

Table I: Comparison of the affinity of tapentadol and morphine at various opioid receptor subtypes, as assessed in binding assays using rat brain membranes (MOR, KOR, DOR) or human recombinant receptors (NOP).

Compound	K_i value (μM)			
	MOR	KOR	DOR	NOP
Tapentadol	0.1	0.9	1.0	> 100
Morphine	0.002	0.17	0.08	> 100

MOR: mu-opioid receptor; KOR: kappa-opioid receptor; DOR: delta-opioid receptor; NOP: ORL1, or nociceptin receptor.

Table II: Comparison of tapentadol and desipramine with respect to neurotransmitter reuptake inhibition, as assessed in rat brain synaptosomes.

Transmitter	K_i value (μM)	
	Tapentadol	Desipramine
Noradrenaline	0.5	0.001
5-HT	2.4	1.4
Dopamine	NE	ND
Choline	39	ND

NE: no effect (5% inhibition at $1 \mu\text{M}$); ND: not determined.

results indicated that the compound has weak anticholinergic activity ($pA_2 = 6.2$).

The *in vivo* functional relevance of NA and 5-HT reuptake inhibition by tapentadol was examined by means of microdialysis probes implanted into the ventral hippocampus of freely moving rats. While morphine at doses of up to 10 mg/kg i.p. did not affect extracellular levels of NA and induced a small increase (approx. 70% above baseline) in extracellular 5-HT levels, tapentadol at doses of up to 10 mg/kg i.p. produced a large, dose-dependent increase in extracellular NA levels (approx. 450% above baseline at 10 mg/kg i.p.) and a much smaller increase in extracellular 5-HT levels (approx. 130% above baseline at 10 mg/kg i.p.). These *in vivo* data correlate well with the *in vitro* data obtained in NA and 5-HT reuptake systems and confirm a much more pronounced functional role of NA compared to 5-HT.

The analgesic properties of tapentadol were investigated in various pain models in mice, rats, rabbits and dogs. These experiments were performed with different routes of administration, including intravenous (i.v.), intraperitoneal (i.p.), oral (p.o.), intracerebroventricular (i.c.v.) and intrathecal (i.t.) routes, and employed a wide range of pain stimuli, including thermal, tactile, chemical and electrical modalities. The pain tests consisted of models of acute nociceptive pain (tail-flick, hot-plate, tooth pulp stimulation and phenylquinone-induced writhing models), acute and persistent inflammatory pain (yeast and formalin models), visceral pain (colorectal distension and mustard oil-induced visceral pain), chronic mononeuropathic pain (chronic constriction injury [CCI]

and spinal nerve ligation [SNL] models) and chronic polyneuropathic pain (vincristine and streptozotocin models). Tapentadol induced effective analgesia in all models (analgesic ED_{50} values compared to morphine are shown in Table III), indicating that it is an analgesic with activity against acute and chronic pain of diverse etiology.

Tapentadol also showed analgesic activity when administered centrally (either i.c.v. or i.t.), suggesting that tapentadol-induced analgesia is (at least partially) centrally mediated. Investigations with tapentadol glucuronide, the major metabolite of tapentadol, in the tail-flick test in mice showed that the glucuronide is devoid of analgesic activity. This supports the notion that tapentadol has no active metabolites.

Interestingly, despite its 50-fold lower MOR affinity compared to morphine, tapentadol was only 2-3 times less potent than morphine after systemic administration. This consistent finding across different models may be due to a better brain penetration of tapentadol, but also suggests that the NA reuptake-inhibitory property of tapentadol potentially interacts with its MOR-agonist property, resulting in more potent analgesia than would be expected solely from its MOR agonism.

To further substantiate the dual mechanism of action of tapentadol, the extent to which its analgesic properties could be blocked by the MOR antagonist naloxone and by the NA receptor antagonist yohimbine was examined. In the rat formalin test, it was found that tapentadol-induced analgesia was reduced by pretreatment with either antagonist, indicating that both opiate and noradrenergic mechanisms are involved in its analgesic effect

Table III: Overview of the analgesic activity of tapentadol¹ and morphine¹ in various animal models of acute and chronic pain.

Pain model	Route of application	ED ₅₀ value (mg/kg)	
		Tapentadol	Morphine
Tail-flick (mouse)	i.v.	4.2	1.4
	p.o.	53.4	18.9
	i.c.v.*	65.0	0.4
Tail-flick (rat)	i.v.	2.2	1.1
	i.p.	10.0	5.8
	p.o.	121	55.7
Tail-flick (dog)	i.v.	4.3	0.7
Hot-plate 48° C (mouse)	i.v.	3.3	1.3
Hot-plate 58° C (mouse)	i.p.	27.7	8.5
Phenylquinone-induced writhing (mouse)	i.v.	0.7	0.4
	p.o.	31.3	4.7
	i.c.v.*	18.4	0.08
Tooth pulp stimulation (rabbit)	i.v.	3.1	2.3
Formalin (phase II) (rat)	i.p.	3.8	0.8
Yeast model (rat)	i.v.	2.0	0.9
	i.p.	10.1	5.6
	i.t.*	56.8	1.9
Colorectal distension-induced visceral pain (rat)	i.v.	5.5	3.5
Mustard oil-induced visceral pain (rat)	i.v.	1.5	1.0
Spinal nerve injury neuropathy (rat)	i.p.	8.3	2.9
Chronic constriction injury neuropathy (rat)	i.p.	13.0	13.8
Vincristine polyneuropathy (rat)	i.p.	5.1	3.4
Diabetic polyneuropathy (rat)	i.p.	8.9	3.0

*Dose in µg/animal. ¹All drug doses for preclinical and clinical testing are for the hydrochloride salt.

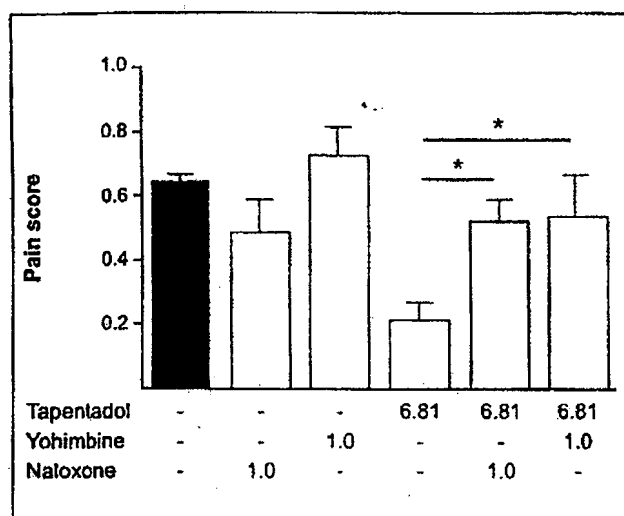


Fig. 1. Antagonism of tapentadol-induced analgesia by the MOR antagonist naloxone and the α_2 -adrenoceptor antagonist yohimbine in the formalin test. The figure shows the pain score (according to a rating scale) during phase II of the test. $n=10$ rats per group. * $p < 0.05$ versus tapentadol treatment. "-" indicates administration of vehicle. Data are shown as mean + S.E.M.

(Fig. 1). Further experiments performed in the SNL model of neuropathic pain demonstrated that the analgesic effect of tapentadol was more sensitive to antagonism by yohimbine than to antagonism by naloxone, whereas the reverse was true for morphine. Taken together, these findings suggest that a prominent part of the analgesic activity of tapentadol in chronic pain states results from its NA reuptake inhibition.

The development of tolerance to the analgesic effects of tapentadol and morphine (at equieffective doses) was investigated in two different pain models in rats—the tail-flick test of acute nociception and the CCI model of chronic neuropathic pain. In both models, tolerance development was considerably delayed with tapentadol compared to morphine (duration of treatment until complete tolerance had developed in the tail-flick and CCI models: tapentadol, 51 and 27 days, respectively; morphine, 21 and 10 days, respectively). These findings may be of relevance for the treatment of chronic pain, because in clinical practice with classical opiates, dose increases may be required due to opioid tolerance.

Physical dependence liability was assessed after precipitated withdrawal (naloxone-precipitated jumping and body weight reduction in mice and rats, respectively) and after spontaneous withdrawal following 3-4 weeks of treatment (diverse withdrawal symptoms in rats). In each model, tapentadol induced less physical dependence than morphine (data from the naloxone-precipitated withdrawal model are shown in Fig. 2).

Pharmacokinetics and Metabolism

In mice, rats and dogs, tapentadol was absorbed rapidly ($t_{max} = 0.5-1$ h) after p.o. administration. The

absolute bioavailability was low and ranged from 3% in dogs to 8% in rats. In male Wistar rats, the mean half-life in plasma was 0.5 h after i.v. administration of 7 mg/kg, but it was clearly longer (> 2 h) after p.o. administration of 300 mg/kg. The clearance was 228 ml/min/kg and the volume of distribution was 10.4 l/kg after i.v. administration. In dogs, the mean terminal disposition half-lives were 0.87 and 3.7 h, respectively, after i.v. and p.o. dosing. The volume of distribution after i.v. administration was 10.9 l/kg and the clearance amounted to 145 ml/min/kg. Protein binding was low in all animal species tested, and ranged from 11% in rabbits to 19% in rats. Comparable protein binding of 19% was found in human plasma.

After p.o. administration of 150 mg/kg [^{14} C]-labeled tapentadol to male Sprague-Dawley rats, the fraction of the radioactive dose recovered in the urine was 69% and that in the feces was 26%, amounting to essentially complete elimination within 48 h. In female rats, approximately 94% of the radioactivity was excreted via urine and 5% via the feces. The high proportion of the dose recovered in urine implies a high extent of absorption of 69-94% of the dose. After oral dosing in male beagle dogs (20 mg/kg), 81% of the dose was recovered in the urine and 18% in the feces within 48 h.

The main metabolic pathway for the elimination of tapentadol in animals and man is phase II metabolism. Glucuronidation was found in mice, rats, dogs and humans; sulfation occurred to a minor extent only in dogs and humans. Phase I biotransformations occurred to a lesser extent, and included hydroxylation of the aromatic ring system with subsequent conjugation and *N*-demethylation, followed by conjugation. *In vitro* investigations on the interaction of tapentadol with cytochrome P-450 enzymes and studies with human hepatocytes indicated no potential for inhibition or induction. Rapid and extensive tissue distribution was found in rats, with kinetics paralleling the conditions in plasma. Radioactivity clearly crossed the blood-brain barrier.

In healthy subjects, tapentadol is rapidly absorbed after a single oral dose, reaching peak serum concentrations within 1-2 h. The calculated pharmacokinetic parameters after i.v. and p.o. administration are summarized in Table IV.

The absolute oral bioavailability of 32% is comparable to that of morphine. The clearance of 1531 ml/min after i.v. administration equals the liver blood flow (1400 ml/min). Dose linearity could be shown after i.v. and p.o. administration of tapentadol in the dose range of 10-80 mg and 75-200 mg, respectively. Steady state after oral administration 4 times daily was reached after approximately 25-30 h. The mean accumulation factor was 1.8, which was determined primarily by the dosing interval and apparent terminal half-life of tapentadol. Basic pharmacokinetic parameters of tapentadol did not change during multiple dosing. A mass balance study with [^{14} C]-labeled tapentadol demonstrated that more than 98% of the radioactivity was recovered in the urine during 48 h. Fecal excretion was negligible ($\sim 1\%$).

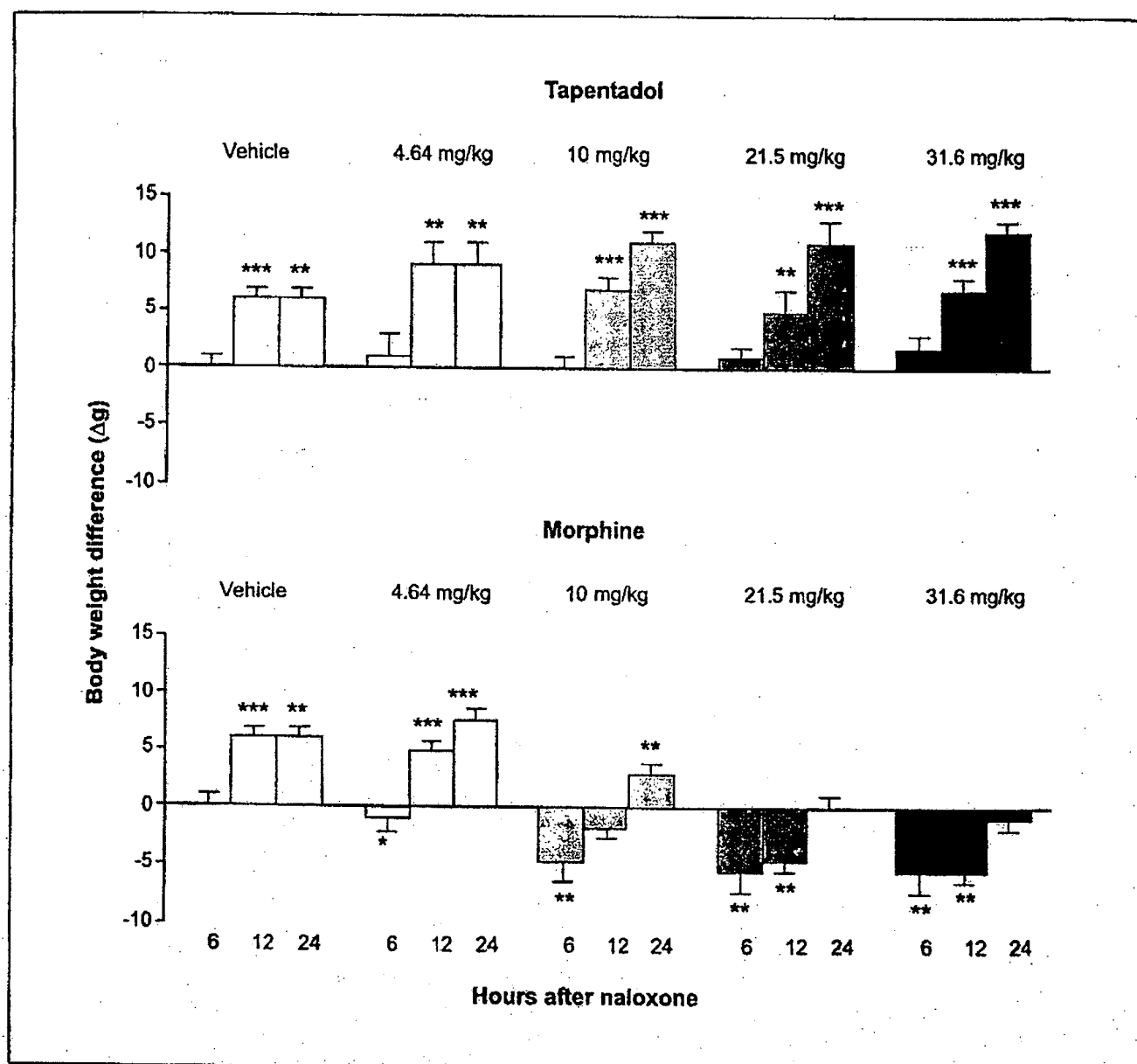


Fig. 2. Comparison of the physical dependence liability of tapentadol and morphine in rats. Data show the effects of naloxone-precipitated withdrawal on body weight measured 6, 12 and 24 h after t.i.d. treatment with tapentadol or morphine during 3 weeks. n=12 rats per group. * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$ versus last day of the treatment regimen. Data are shown as mean + S.E.M.

Table IV: Summary of pharmacokinetic parameters after a single i.v. infusion and oral administration of tapentadol in 24 fasted male volunteers. Data are presented as mean values and refer to tapentadol (free base).

Parameter	15-min infusion	IR oral
	40 mg	100 mg
AUC (ng.h/ml)	379	314
C _{max} (ng/ml)	243	78
t _{max} (h)	0.26	1.2
t _{1/2} (h)	4.1	4.9
CL (CL/f) (ml/min)	1531	5007
V _z (V _{zt}) (l)	540	2127
F (%)	—	32

IR: immediate release; C_{max}: peak plasma concentration; t_{max}: time to C_{max}; t_{1/2}: terminal half-life; CL: total clearance; V_z: volume of distribution; F: bioavailability.

Safety

Tapentadol induced only weak emesis-like behavior in the ferret at doses ranging from 10 to 31.6 mg/kg i.p. Approximately 20% of the animals in both the low- and high-dose groups exhibited emesis with food expulsion. Compared with low doses of morphine (0.125-0.5 mg/kg s.c.), tapentadol was associated with a substantially lower incidence of retches and vomits per animal (Fig. 3), and the duration of these effects was shorter.

The gastrointestinal-inhibitory activity of tapentadol was also relatively weak compared to morphine. In mice, tapentadol and morphine inhibited charcoal transit from the stomach to the cecum with ED_{50} values of 28.1 and 5.9 mg/kg i.p., respectively, and inhibited PGE_2 -induced diarrhea with ED_{50} values of 10.3 and 1.1 mg/kg i.p., respectively.

Tapentadol dose-dependently reduced spontaneous respiratory frequency in conscious rats following i.v. bolus injection of 4.64-14.7 mg/kg. In a rat plethysmography model, i.v. tapentadol reduced the respiratory minute volume at 18 mg/kg, but not at 2 and 6 mg/kg. CO_2 -induced stimulation of respiratory frequency was less potently inhibited by tapentadol than by morphine ($ED_{50} = 0.71$ and 0.23 mg/kg i.v., respectively). Tapentadol induced an increase in arterial pCO_2 in rats, but again, with lower potency and efficacy than morphine. Daily treatment with tapentadol or morphine resulted in complete tolerance to the respiratory depressive effect within 22 days, indicating that, with respect to respiratory depression, tapentadol does not show delayed tolerance development compared to morphine (such as that seen with respect to analgesia).

Tapentadol weakly inhibited the I_{Kr} current in Chinese hamster ovary (CHO) cells, with an IC_{50} of 36 μM . The O-glucuronide, the N-demethyl and the sulfate metabolites of tapentadol were even less active ($IC_{50} > 250 \mu M$). Tapentadol slightly shortened the action potential duration at 10 and 100 μM in guinea pig papillary muscle. In isolated spontaneously beating atrial preparations

and electrically stimulated papillary muscles of guinea pigs, tapentadol exerted negative chronotropic and negative inotropic effects only at concentrations higher than 100 μM .

In conscious rats, tapentadol (4.64-14.7 mg/kg i.v.) induced transient (10-15 min) increases in arterial blood pressure and heart rate. In anesthetized rabbits, i.v. bolus injections of 1-10 mg/kg tapentadol led to dose-dependent decreases in heart rate and arterial blood pressure and to a negative inotropic effect. Tapentadol did not increase the heart rate-corrected $Q-T_c$ time. In conscious dogs, i.v. infusion of tapentadol at doses of 3, 6 and 9 mg/kg produced dose-related, reversible increases in arterial blood pressure, heart rate and cardiac output. The $Q-T$ time was decreased in parallel to the increase in heart rate. In anesthetized dogs, i.v. infusion of tapentadol at doses of 0.5, 1.5 and 4.5 mg/kg induced a dose-dependent hypotensive effect. Tapentadol did not affect $Q-T$ or $Q-T_c$ times in anesthetized dogs.

Acute toxicity studies were performed in rats and mice after i.v. and p.o. administration. Clinical signs of toxicity included hyperexcitability, irregular respiratory activity and convulsions. LD_{50} values after p.o. administration ranged from approximately 350 mg/kg in mice to > 1000 mg/kg in rats; after i.v. administration, LD_{50} values were approximately 45 mg/kg in both species.

In repeated-dose toxicity studies, tapentadol was administered i.v. and p.o. for 4 weeks to rats and for 2 weeks to dogs. In addition, the toxicological profile was evaluated in long-term studies with a treatment period of 13 and 52 weeks in dogs and 26 weeks in rats. In these studies, treatment-related clinical signs were characterized by CNS-related behavioral disorders, such as fearfulness and increased excitability, or sedation at higher dose levels. Single episodes of convulsions at the maximum tolerated dose (MTD) level and isolated incidences of vomiting were observed in dogs only. There was no indication of specific organ toxicity in either species.

The overall weight of evidence from a battery of *in vitro* and *in vivo* mutagenicity tests demonstrates that

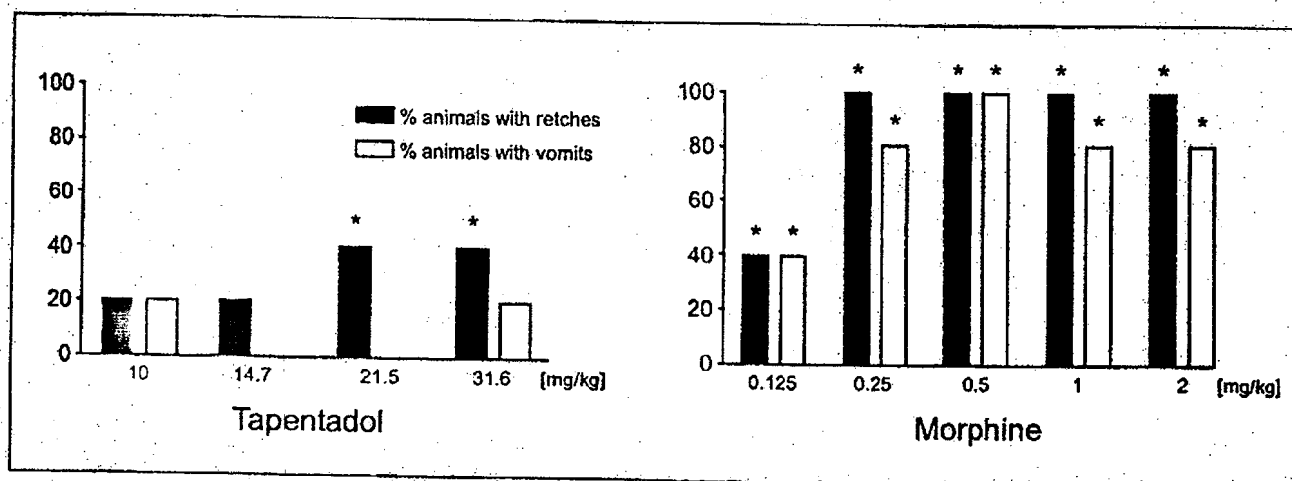


Fig. 3. Comparison of the liability of tapentadol (i.p.) and morphine (s.c.) to induce emesis in ferrets. Data represent the percentage of animals showing retches and/or vomits. $n=10$ ferrets per group. * $p < 0.05$ versus vehicle control.

tapentadol has no mutagenic potential of relevance for human use. Embryotoxicity studies in rats and rabbits showed that it has no teratogenic properties; male and female fertility was not affected.

Following single and multiple doses in clinical trials, tapentadol exhibited a good safety and tolerability profile. The adverse event profile after single oral doses was well within the expected range for centrally acting substances. The most frequently reported adverse events were nausea, dizziness, vomiting, somnolence, vertigo and headache. At presumed equianalgesic doses, tapentadol appeared to have an improved tolerability profile compared to tramadol and morphine with regard to nausea and vomiting. Multiple doses of 25 and 50 mg tapentadol given every 6 h were also well tolerated. The most frequently reported adverse events in patients treated over 5 days were headache, nausea, dizziness and sleep disturbance.

Following orthopedic surgery, multiple doses of tapentadol 50 and 116 mg were administered over a period of 5 days. Compared to oxycodone 10 mg, an equianalgesic dose of 58 mg tapentadol showed a more favorable tolerability profile, with a lower frequency of nausea, dizziness, vomiting and constipation. In the case of the effective higher dose of tapentadol, the frequency of nausea and constipation was lower compared to oxycodone 10 mg, while the frequency of dizziness and somnolence was higher. Tapentadol did not have any clinically relevant effects on laboratory variables, ECGs or vital signs, including respiratory function, pulse rate and blood pressure.

Conclusion

Tapentadol is a novel, orally available, centrally acting analgesic that combines MOR agonism and NA reuptake inhibition in a single molecule, independent of metabolic activation. Its dual mode of action translates into a broad and effective analgesic profile, as assessed in a variety of animal models of acute and chronic pain, with both mechanisms of action contributing to its analgesic effects. Moreover, tapentadol has a lower propensity to produce tolerance, physical dependence, and may have an improved adverse event profile (in particular, with respect to gastrointestinal side effects) compared to morphine. This is presumably due to its nonopioid component, which results in higher analgesic efficacy than expected from its lower affinity for the MOR. Based on these attributes, it is expected that tapentadol will offer an improved therapeutic option for the treatment of moderate to severe pain.

Source

Grünenthal GmbH (DE).

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EXPERT OPINION

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Mechanistic and functional differentiation of tapentadol and tramadol

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Introduction: Many opioid analgesics share common structural elements; however, minor differences in structure can result in major differences in pharmacological activity, pharmacokinetic profile, and clinical efficacy and tolerability.

Areas covered: This review compares and contrasts the chemistry, pharmacodynamics, pharmacokinetics, and CNS 'functional activity' of tapentadol and tramadol, responsible for their individual clinical utilities.

Expert opinion: The distinct properties of tapentadol and tramadol generate different CNS functional activities, making each drug the prototype of different classes of opioid/nonopioid analgesics. Tramadol's analgesia derives from relatively weak μ -opioid receptor (MOR) agonism, plus norepinephrine and serotonin reuptake inhibition, provided collectively by the enantiomers of the parent drug and a metabolite that is a stronger MOR agonist, but has lower CNS penetration. Tapentadol's MOR agonist activity is several-fold greater than tramadol's, with prominent norepinephrine reuptake inhibition and minimal serotonin effect. Accordingly, tramadol is well-suited for pain conditions for which a strong opioid component is not needed—and it has the benefit of a low abuse potential; whereas tapentadol, a schedule-II controlled substance, is well-suited for pain conditions requiring a strong opioid component—and it has the benefit of greater gastrointestinal tolerability compared to classical strong opioids. Both drugs offer distinct and complementary clinical options.

Keywords: analgesia, efficacy, MOR-NRI, synergy, tapentadol, tramadol, translational drug design

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1. Introduction

In the history of medicinal chemistry and pharmacology in drug discovery, chemists have created a variety of ways to describe a chemical structure and to characterize its relevant feature, and pharmacologists have created a variety of ways to describe differences in drug potency, affinity and intrinsic activity at receptor sites, and efficacy [1]. Both histories have converged on the recognition of the critical importance of discriminating drugs based on 'functional activity,' rather than on superficial similarities in chemical structure or *in vitro* assays.

The late writer and chemist Primo Levi complained in 1984 that there were only three acceptable ways to describe a molecule and that none of them were very good: i) the ambiguous molecular formula, ii) the nonlexical chemical graph, and iii) the (often obscure) chemical name [2]. Yet, because these were the only ways that chemists had at the time to describe a molecule's 'constitution,' they dominated the approaches to predicting what a molecule would do. These approaches were based on the 2D

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Article highlights.

- Tapentadol has an open-chain structure in the place of tramadol's cyclic structure, resulting in distinct chemical and biological properties.
- Both drugs combine, in different ways, opioid and nonopioid activities that act synergistically to produce analgesia. As they do so in mechanistically distinct ways, the resulting clinical attributes are different.
- Tapentadol, in a single molecule, combines relatively strong μ -opioid receptor agonism and norepinephrine reuptake inhibition, but has no relevant functional serotonin reuptake inhibition and no analgesically-active metabolite. The two enantiomers of tramadol contribute to different mechanisms (i.e., weak μ -opioid receptor agonism, as well as neuronal norepinephrine and serotonin reuptake inhibition); an analgesically active μ -opioid metabolite contributes to an extent dependent on dose and ADME factors.
- With much greater potency at the μ -opioid receptor compared to tramadol, tapentadol has a CNS functional opioid activity several-fold greater than tramadol's; its norepinephrine reuptake inhibition is the same or a little greater than tramadol's; and its serotonin activity is much reduced compared to that of tramadol.
- Tapentadol mainly undergoes Phase II metabolism (glucuronidation), whereas tramadol primarily undergoes Phase I (CYP2D6 and CYP3A4) metabolism.
- Tapentadol's opioid and norepinephrinergic activities are both present in the parent molecule; tramadol's opioid activity is mainly expressed in its primary metabolite, whereas its monoaminergic activity is primarily present in its parent molecule.
- Tapentadol's greater functional μ -opioid activity gives rise to potency and efficacy comparable to strong opioids; tramadol is widely used for multiple pain types where a strong opioid component is not needed or desired.
- Tapentadol is a controlled substance with reduced gastrointestinal adverse effects compared to classical strong opioids; tramadol has a history of long-term use and low abuse potential.
- Due to its unique features, it has been proposed that tapentadol belongs to a new pharmacological class, MOR-NRI.

This box summarizes key points contained in the article.

(two-dimensional) structural formula, only indicating stereochemistry with stereochemical descriptors. It is now known that this presentation of a chemical structure is an oversimplification that only focuses on the connectivity and binding mode of the atoms and, to some extent, their spatial arrangement. At the time, this was necessary for printed materials, but modern computers now allow greater flexibility to visualize 'lock-and-key fit' and the importance of 3D (three-dimensional) visualization of structure. To illustrate the limitations and potential pitfalls of the now archaic approach of comparing the 2D carbon skeleton (i.e., taking only the ring systems and the linkers connecting the ring systems into consideration [3]), tramadol would be erroneously compared to

the NSAID (non-steroidal anti-inflammatory drug) diflunisal, because both drugs have the same generalized carbon scaffold (wherein two ring systems are connected without a spacer group). Based on this type of chemotypic analysis, as described by Hu *et al.* [4], tramadol and diflunisal should act by common pharmacological mechanisms, which of course they do not.

Even SMILES (simplified molecular input line entry specification) [5], which was developed by David Weininger shortly after Levi's lament and intended to be a real lexicographic description, only facilitated methods that relied on the counting of elements of composition, chemical rules of thumb, classification algorithms, drug-like filters (e.g., the ubiquitous 'rule of five' [6]), 2D QSAR (quantitative structure-activity relationship) or molecular fingerprints. Whereas chemists may have elaborated beyond the elemental to include graph-related properties (such as aromaticity, hydrophobicity, hydrophilicity, hydrogen bond donors and acceptors, etc.), these are seldom fundamental and are often simply opinions on how molecules behave [1]. It is now universally recognized that the different types of interactions between molecules and a biological target strongly depend on the spatial arrangement of molecular fragments within the target macromolecule [7]. Thus 3D shape must be considered in order to predict essential aspects of the pharmacological activity of a molecule.

Therefore in the first section of this review, we describe how the 3D shape of tapentadol was rationally designed to produce a new compound having distinct pharmacodynamic and pharmacokinetic properties in order to achieve specific clinical goals.

Similar to the historical development of approaches to best (most fully) describe the chemical attributes of drugs, there has been equivalent development of approaches to best describe the pharmacological attributes of drugs. One of the earliest, because of its simplicity, was to use 'potency' (the amount of a drug required to produce a defined level of effect), typically reported as an ED_{ϵ} where ϵ is a specified level of effect. The limitations of such a measure are readily apparent, since such a measure is highly dependent on factors unrelated to the drug's mechanism of action. A clear example is loperamide, which is mechanistically a strong opioid, but is devoid of CNS (central nervous system) effects when administered orally, because it does not cross the blood-brain barrier. A more mechanistic measure of a drug's pharmacological attributes was devised and termed 'affinity' (the strength of attraction between a drug and its target) and is typically reported as a K_i value (for a review of the historical development of this concept [8]). Such a measure, however, does not account for the result of the binding, since antagonists have affinity for the drug's target site, but do not produce the effect. Therefore, in order to describe target activation, measures such as 'intrinsic activity' or 'intrinsic efficacy' at the target site (receptor) were introduced. The most comprehensive comparison of two drugs utilizes a composite of all of these measures as manifested in each drug's 'functional activity' (defined as the ratio of the estimated brain

concentration to the relevant functional EC_{50} or K_i value at a specified receptor or transporter site) in the desired therapeutic application—in this case, antinociception (in animals) or analgesia (in humans).

Therefore in the second section of this review, we describe how the differences in the CNS functional activity of tapentadol and tramadol (based on the differences in their pharmacodynamic, pharmacokinetic, and functional activity characteristics) correlate with their clinical features and common uses. Escalating the dose of tramadol in an effort to match tapentadol's greater opioid activity is not a clinically feasible option because disproportionately more of the weaker opioid parent drug crosses the blood–brain barrier than does its stronger opioid metabolite (*O*-desmethyl tramadol). In fact, in the same models, the disparity gets progressively larger as the dose of tramadol is increased [9].

The significantly different pharmacodynamic, pharmacokinetic, and CNS functional activities of tapentadol and tramadol are consistent with, and provide the basis for understanding, the different clinical profiles of these two centrally acting analgesics.

2. Chemical differentiation of tapentadol from tramadol

Based on elucidation of the favorable aspects of the multimodal analgesic mechanism of action of racemic cyclohexyl analgesics (of which tramadol was one representative), a research program was initiated to design a new class of opioid/nonopioid analgesics that would combine MOR (μ -opioid receptor) agonism and norepinephrine reuptake inhibition, with minimal serotonergic activity. It was also desired that both activities would reside in a single parent molecule that does not require metabolic activation via the cytochrome P450 system.

2.1 The discovery of tapentadol

The 3D molecular shape of tapentadol is very different from that of tramadol, which manifests itself in the different pharmacological profiles of the two analgesics. In the following sections, these differences are described in more detail, including the chemical distinction between the cyclic structure of tramadol and the open-chain structure of tapentadol (Figure 1), resulting in reduced molecular complexity and a stronger CNS functional activity that is primarily derived from its two intrinsically synergistic mechanisms of analgesic action.

2.2 The dimethylaminomethyl fragment

The dimethylaminomethyl moiety is a significant part of the pharmacophore that is needed for interaction with MOR and interaction with the monoamine transporter system [10]. Demethylation is a metabolic pathway leading to CH_2NH (CH_3) and CH_2NH_2 derivatives that lack significant analgesic activity [11,12]. Increasing the size of the nitrogen substituent or cyclic substitution also leads to inactive compounds. The dimethylaminomethyl fragment, therefore, appears to be essential for analgesic activity for both drugs.

2.3 The role of relative stereochemistry

Tramadol and tapentadol contain two chiral carbon atoms. Consequently, for both molecules, four stereoisomers exist as two diastereomeric pairs of enantiomers. However, tramadol is a racemate, whereas tapentadol is a pure enantiomer. The relative stereochemistry is critical for biological activity. In both cases, only the (*R,R*) and (*S,S*) isomers display analgesic activity, whereas the diastereoisomers are relatively inactive. The stereochemical requirements and dimethylaminomethyl fragment are the only common relationships between tapentadol [(–)-(1*R*,2*R*)-3-(3-dimethylamino-1-ethyl-2-methyl-propyl)-phenol hydrochloride] and tramadol [(1*RS*,2*RS*)-2-[(dimethylamino)methyl]-1-(3-methoxyphenyl)cyclohexanol] hydrochloride.

2.4 Cyclic core structure versus open-chain molecule

Several drugs possess cyclic aliphatic ring systems connected via linkers with other aromatic or hetero aromatic groups [13]. However, in the lead optimization phase, a cyclic ring system is typically modified by changing the ring size and introducing hetero atoms (such as nitrogen, oxygen, or sulfur) as well as introducing additional substituents in order to optimize desired hydrophobic or non-hydrophobic interactions with the biological target, thereby leading to an increase in the potency of a given lead structure. As a consequence, the cyclic structure is retained in many lead optimization programs due to the entropic and enthalpic balance of the thermodynamics of binding [14,15]. Cyclic structures generally have the advantage of decreasing the entropic proportion of the binding energy compared with open-chain molecules, leading to more flexible derivatives with greater ligand efficiency [16]. Additionally, many examples are known wherein an open-chain analog of a given drug loses biological activity completely; for instance, the open-chain analog of diazepam is completely inactive [17]. In the course of the development of tapentadol, it was found that opening the cyclohexane ring system led to active compounds while conserving the relative stereochemistry. However, the activity of the molecules was strongly dependent on the length of the side chain. It was found that a methyl group and an ethyl group at critical carbon atoms were optimal in the general formula. The preference of the pentyl chain in tapentadol compared with analogs containing the hexyl chain (comparable to the cyclohexane core ring of tramadol) was not predictable by any *in silico* tool available at the time and can still not be explained by usual structure–activity relationships.

2.5 A drug with an active metabolite versus a drug without one

The introduction of a phenolic hydroxy group instead of an aromatic methoxy group results in a dramatic change in pharmacological activity [10]. Whereas tramadol is a racemate with an active racemic metabolite (*O*-desmethyl tramadol, M1)

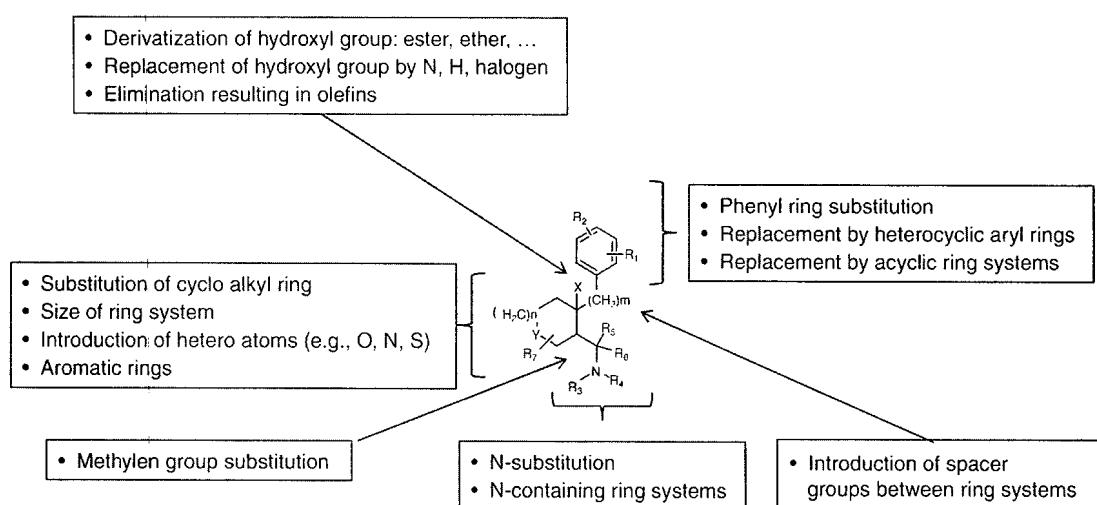


Figure 1. Summary of chemical modifications leading to the discovery of tapentadol. Shown is a generic structure of the class of cycloalkyl-based analgesic drugs. Tramadol is represented by $R_1 = 3\text{-OCH}_3$, $R_2 = \text{H}$, $R_3 = R_4 = \text{CH}_3$, $R_5 = R_6 = \text{H}$, $R_7 = \text{H}$, $n = 1$, $m = 0$, $Y = \text{CH}_2$, and $X = \text{OH}$.

that is generated following cytochrome P450 (CYP2D6)-mediated *O*-demethylation, tapentadol does not have analgesically active metabolites (i.e., both of its mechanisms of action reside within the parent molecule).

The enantiomers of open-chain phenolic structures showed increased analgesic activity compared to the cyclic tramadol-derived analogs. Consequently, the enantiomers were investigated separately in the optimization process described below.

2.6 Racemate versus pure enantiomer

In past decades, the pharmacopoeia was dominated by racemates [18]; however, since the emergence in the 1980s of new technologies that allowed the preparation of pure enantiomers in significant quantities, the awareness and interest in the stereochemistry of drug action has increased. The advances in stereoselective bioanalysis led to new awareness of the importance of stereoselective pharmacodynamics and pharmacokinetics, enabling the differentiation of the relative contributions of enantiomers to overall drug action. These factors have led to an increasing preference for selection of single enantiomers by both the pharmaceutical industry and regulatory authorities. Enantiomeric purity is now a primary objective in the design, discovery, development, launching, and marketing of new drugs [19].

As a consequence of this changing climate toward drug chirality, pure enantiomers were used for further optimization. Subsequently, it was found that the MOR affinity of the enantiomer acting on the norepinephrine transporter was increased, and in the following steps, modifications were made to increase this MOR affinity.

2.7 Replacement of the aliphatic hydroxyl group

It is known for many drugs that their aliphatic hydroxyl group is essential for pharmacological activity [20].

Derivatization by introducing ester or ether groups in this position led to the loss of analgesic activity. However, replacement of the tertiary hydroxyl group by either fluorine or hydrogen resulted in a significant increase of MOR affinity for both enantiomers. The fluorine derivatives were not further developed due to physicochemical stability issues. Critically, the hydrogen derivative was found to have both activities in one molecule. While retaining the norepinephrine reuptake inhibition (NRI) component, the MOR agonism component was increased to achieve potent analgesic activity without the prominent serotonin reuptake inhibition (SRI) effect present in tramadol. Chemical innovations introduced in the development of tapentadol are summarized in Figure 2.

2.8 Tapentadol as a rationally designed polypharmacological ligand

Increasing evidence demonstrates that many pharmaceutically important compounds elicit their effects through binding to multiple targets. This so-called 'directed polypharmacology' is impacting conventional drug discovery and rational drug design strategies [21]. The single-target focus traditionally dominated compound optimization efforts, and a high degree of target specificity was typically considered a desirable goal of drug candidates. Systems biology, however, has revealed networked physiological systems with convergent, divergent, and integrated signaling pathways that involve extensive crosstalk among these pathways. The reduction of drug discovery to a single target is now seen to be a gross oversimplification that unduly minimizes the complexity of the pathophysiology [22]. Drug programs that assume a single-target mechanism, particularly for the CNS, can have extremely low success rates, with early hits often leading to costly failures at

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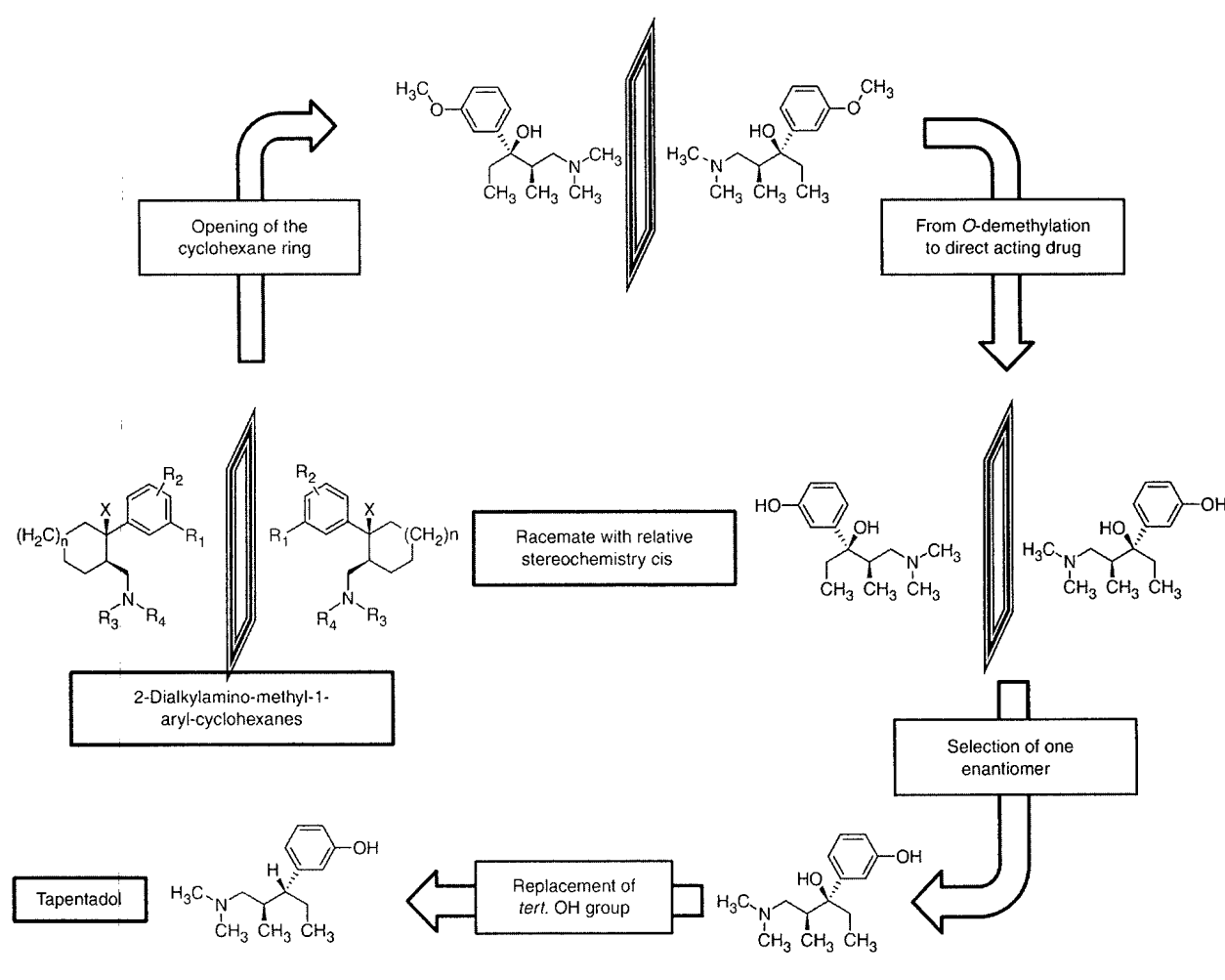


Figure 2. Chemical innovations introduced in the development of tapentadol.

the clinical stage. Furthermore, such drugs can produce excess adverse effects because of the high doses needed by single-mechanism agents. In many cases, the adverse effects contribute to a termination of drug intake, sometimes resulting in disease relapse, and major problems such as chronic pain remain unsolved [23]. In recent years, it has been increasingly appreciated that multi-pathophysiological medical conditions are most likely best treated by complementary multi-modal mechanisms of action. Hence, polypharmacology is beginning to be regarded as a general drug discovery principle—the so-called concept of Designed Multiple Ligands—that influences compound design, optimization, and evaluation [24,25].

3. Pharmacological differentiation of tapentadol from tramadol

The pronounced 3D differences in chemical structure of tramadol and tapentadol translate into a number of substantial functional differences.

3.1 Differences in opioid receptor binding affinity and functional activity

As shown in Table 1, tapentadol binds to recombinantly-expressed human MOR (hMOR) with an affinity (K_i value) of 0.16 μM [26]. For tramadol, its enantiomers, or its M1 (*O*-desmethyl) metabolite and enantiomers, a range of values has been reported [27,28]. From the most recent, the parent form of tramadol exhibits low hMOR affinity with a K_i value of 2.4 μM , whereas its (+)M1 metabolite exhibits much higher affinity with a K_i of 0.0034 μM [28]. Thus, the parent form of tramadol exhibits about 15-fold lower affinity for hMOR than does tapentadol and about 700-fold lower affinity than its (+) M1 metabolite. In comparison, tapentadol binds with nearly 50-fold lower affinity for hMOR than does the (+)M1 metabolite of tramadol. However, these binding numbers may underestimate the pharmacological strength of the interaction, as shown below when one measures functional activity.

In contrast to its lower binding affinity, the functional activity of tapentadol in the agonist-stimulated [^{35}S]GTP γ S binding assay in cells recombinantly expressing hMOR is similar

Table 1. *In vitro* evaluation of the binding and functional activity of tapentadol, tramadol, and tramadol enantiomers and metabolites at rat and human MOR, NET, and SERT.

	MOR K_i Binding affinity (μM)	hMOR EC_{50} [^{35}S]GTP γS binding (μM)	hNET K_i Functional uptake (μM)	hNET K_i Binding affinity (μM)	hSERT K_i Binding affinity (μM)	rNET K_i Functional uptake (μM)	rSERT K_i Functional uptake (μM)
Tapentadol	0.16 [§]	0.67 [§]	0.75 [¶]	8.8 [§]	5.28 [§]	0.48 [§]	2.37 [§]
Racemic Tramadol	2.4 [*]	Inactive [#]	NA	14.6 [¶]	1.19 [‡]	0.78 [‡]	0.99 [‡]
(+) Tramadol	1.3 [‡]	NA	NA	NA	0.87 [¶]	2.51 [‡]	0.53 [‡]
(-) Tramadol	24.8 [‡]	NA	1.08 [¶]	NA	NA	0.43 [‡]	2.35 [‡]
Tramadol (+)M1	0.0034 [*]	0.86 [*]	NA	NA	NA	14.4 [#]	2.98 [#]
Tramadol (-)M1	0.24 [*]	> 50 [*]	NA	NA	NA	0.86 [#]	17.7 [#]

^{*}Affinity at human MOR measured by naloxone competitive inhibition [28].

[†]Affinity measured by competitive inhibition in rats [69].

[‡]Affinity at human MOR measured by naloxone competitive inhibition [26].

[¶]Hertrampf and Englberger (unpublished observations).

[#]Rat brain homogenates (Codd et al. [unpublished observations]).

h: Human; MOR: μ -opioid receptor; NA: Not available; NET: Norepinephrine (noradrenaline) transporter; r: Rat; SERT: Serotonin transporter.

to that of the higher-affinity (+)M1 metabolite of tramadol (tramadol parent displays no detectable functional activity) (Table 1) [26,28]. This highlights the importance of comparing drugs based on their functional activity rather than on an indirect measure such as binding affinity (which does not take into account intrinsic activity, target access, etc.). Just as a superficial similarity in 2D chemical structure is an unreliable indicator and underestimates the differences between the biological effects of tapentadol and tramadol, so too does a comparison based on *in vitro* binding affinity alone.

3.2 Differences in NET and SERT binding affinity and functional activity *in vitro*

Regarding interactions with the monoaminergic transporters NET and SERT, tapentadol binds to human NET (hNET) and SERT (hSERT) with K_i values of 8.8 [26] and 5.28 μM , respectively, whereas the tramadol parent binds to these targets with K_i values of 14.6 and 1.19 μM , respectively (Hertrampf & Englberger, unpublished observations) (Table 1).

In terms of the functional inhibition of these targets, tapentadol blocks norepinephrine uptake by hNET with a K_i value of 0.75 μM and serotonin uptake by rat SERT (data not available for the human ortholog) with a K_i value of 2.37 μM . In comparison, (-)-tramadol blocks the function of the hNET with a K_i value of 1.08 μM , and (+)-tramadol blocks rSERT with a K_i value of 0.53 μM , respectively (Table 1). Both tramadol M1 metabolite enantiomers are less potent at these transporters and achieve lower brain concentrations (see below) compared with their respective parents, thereby limiting their functional contributions to these mechanisms. Thus, tapentadol is slightly *more* potent than tramadol in blocking hNET and nearly *fivefold less* potent than tramadol in blocking rSERT.

Again, the above mechanistically insightful results highlight the importance of comparing drugs based on their functional activity rather than on binding affinity or other indirect measures. Only the former provides the added dimension

that elucidates the true nature and extent of the individual properties of two drugs, and hence of their differences.

In summary, the *in vitro* receptor binding and *in vitro* functional assays demonstrate that tapentadol and tramadol (including its M1 metabolite) are substantially different with respect to their MOR agonism, serotonin reuptake inhibition (tapentadol greater at the former and lesser at the latter compared with tramadol) and in the resulting *in vivo* effects. As discussed in the following sections, the differences are magnified *in vivo*, because of two factors: i) differences in functional activity *in vivo*, and ii) because of limited distribution of tramadol (+) M1 to the brain.

3.3 Differences in monoaminergic functional activity *in vivo*

The *in vivo* differences in NET and SERT profiles of tapentadol and tramadol become evident in microdialysis measurements in the ventral hippocampus in the rat. As shown in Figure 3, in this assay, tramadol produces large dose-dependent increases in both norepinephrine (about fivefold of baseline) and serotonin (about five- to sixfold of baseline) within its analgesic dose range [29]. In contrast, tapentadol produces a similarly large dose-dependent increase in extracellular norepinephrine levels (about five- to sixfold of baseline), but much lower increase in extracellular serotonin levels compared to tramadol (about twofold of baseline) within its analgesic dose range [26].

3.4 Differences in analgesic efficacy and the impact of metabolism

The substantial potency difference between tapentadol and tramadol was first established in animal models of pain. Across a variety of assays, tapentadol is consistently two to five times more potent than tramadol (e.g., ED_{50} value of 2.2 and 9.6 mg/kg i.v., respectively, in the rat tail flick test and ED_{50} values of 1.65 and 3.5 mg/kg i.v., respectively, in the rat spinal nerve ligation [SNL] model). This potency

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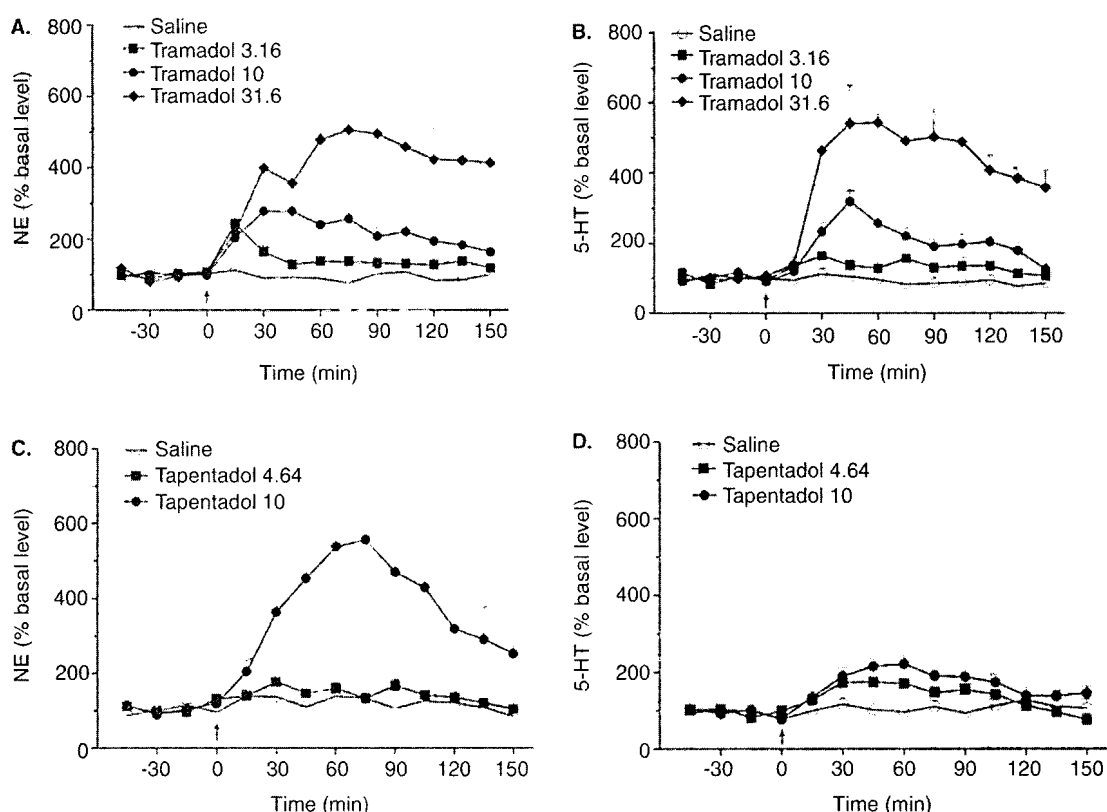


Figure 3. Microdialysis in the ventral hippocampus of freely moving rats after i.p. administration of tramadol (A, B) or tapentadol (C, D). Tramadol produced clear increases in extracellular levels of NE (A) and 5-HT (B). Tapentadol produced a clear increase in NE levels (C), but only a minor increase in 5-HT levels (D). Doses are indicated as mg/kg i.p.

Tramadol data reprinted from [29] with permission from Elsevier.
Tapentadol data adapted from [26].

difference cannot be explained by the *in vitro* potency data alone (see above for details), because the EC_{50} of (+)M1 at MOR (0.86 μ M) is similar to that of tapentadol (0.67 μ M), and the K_i of tapentadol inhibition of hNET (0.75 μ M) is similar to that of tramadol (1.08 μ M).

To further analyze functional analgesic activity, we determined the 'CNS activity' (defined as the ratio of the estimated brain concentration in humans divided by the relevant functional EC_{50} or K_i value at the receptor or monoaminergic transporter) of tapentadol and tramadol plus its active metabolite M1. Specifically, we calculated the relative ratio of the human plasma steady-state C_{max} and C_{avg} (AUC/ τ) values for tapentadol (100 mg every 4 h) and tramadol (200 mg b.i.d.) at steady state to the EC_{50} (MOR) or K_i (NET and SERT). For tapentadol, C_{max} = 145 ng/mL and AUC = 3,071 ng $\times$ h/mL (Terlinden *et al.*, unpublished observations). For (+)tramadol, C_{max} = 323 ng/mL (1.2 μ M) and AUC = 2,784 ng $\times$ h/mL (C_{avg} = 0.4 μ M), and for (-)tramadol, C_{max} = 290 ng/mL (1.1 μ M) and AUC = 2,227 ng $\times$ h/mL (C_{avg} = 0.4 μ M) [30]. For (+)M1, C_{max} = 61 ng/mL and AUC = 697 ng $\times$ h/mL, and for (-)M1, C_{max} = 81 ng/mL and AUC = 761 ng $\times$ h/mL [30]. For MOR, the EC_{50} values for tapentadol and tramadol (+)

M1 were based on agonist-stimulated [^{35} S]GTP γ S binding assay in cells recombinantly expressing human MOR. For NET, the K_i values were based on human functional transporter assays for tapentadol and (-)tramadol. For SERT, the K_i values were based on rat functional transporter assays for tapentadol and (+)tramadol. The potency of tapentadol measured in the rat functional NET assay (0.5 μ M) is about the same as that in the human (0.7 μ M); we assume that the same approximation is true for rat and human SERT. Notwithstanding differences in brain penetration as a function of dose, we also assumed that the plasma concentrations of (+) and (-)tramadol, tramadol (+) and (-) M1 and tapentadol represent a reasonable estimate of extracellular fluid or brain concentrations, based on microdialysis studies (Beier, Terlinden *et al.*, unpublished observations) [9]. Thus, the ratio of brain C_{max} of tapentadol to the EC_{50} at MOR (0.71 μ M/0.67 μ M = 1.06) is much larger than the ratio for tramadol (+)M1 (0.24 μ M/0.86 μ M = 0.28), thus leading to a much greater μ -opioid effect than tramadol (+)M1. Similar calculations of the ratio of brain C_{max} to the functional K_i for NET and SERT revealed approximately similar activity of tapentadol and the more NRI-selective (-)-enantiomer of tramadol at the NET and negligible activity of tapentadol at the SERT. This

fundamental distinction and differentiation between the two drugs is illustrated in Figure 4.

The 'CNS activity' ratios of tapentadol are about the same whether calculated using C_{max} or C_{avg} in contrast to tramadol (Figure 4A vs 4B). In either case, the CNS opioid activity of tapentadol is much greater than that of tramadol (3.73- to 6.91-fold). The contribution of NET inhibition is the same or even greater for tapentadol than for tramadol (0.94- to 2.60-fold). But tapentadol's SERT inhibition is only about 10–25% that of tramadol's, demonstrating the success of the medicinal chemistry effort to reduce this activity in creating a new drug.

3.5 Differences in the contribution of NRI and SRI activities to efficacy

The contribution of norepinephrinergic activity and the lack of relevant serotonergic activity of tapentadol were confirmed in a number of animal pain models. For example, Schröder *et al.* (2010) showed that the dose-response curve for the antinociceptive effect of tapentadol in a low-intensity tail flick model and for the antihypersensitive effect in a SNL model was shifted to the right by the α_2 -adrenoceptor antagonist yohimbine (increase of the ED_{50} value by 1.7-fold in the acute nociceptive pain model and by 4.7-fold in the chronic neuropathic pain model), but not by the 5-HT₂ receptor antagonist ritanserin [31]. An antagonism of the tapentadol effect by yohimbine and a lack of antagonism by ritanserin has also been observed in the CFA (complete Freund's adjuvant)-induced hyperalgesia model of chronic inflammatory pain [32]. In contrast, both the norepinephrinergic and serotonergic mechanisms have been demonstrated to contribute to the analgesic efficacy of tramadol. The antihypersensitive effect of tramadol in the SNL (spinal nerve ligation) model is reduced by both yohimbine and ritanserin (Christoph *et al.*, unpublished observations). Raffa *et al.* (1992) have also shown that the antinociceptive effect of intrathecal tramadol in a tail-flick model is blocked by both yohimbine and ritanserin [33].

3.6 Differences in source of synergy

A recent study has demonstrated that the two mechanisms of action of tapentadol show a very pronounced intrinsic synergy with respect to antinociceptive activity in a low-intensity tail-flick test in the rat [34]. In that study, indirect evidence was also obtained for an intrinsic antihypersensitive synergy in a SNL model. To our knowledge, this was the first demonstration of two mechanisms of action (MOR agonism and NRI) within one molecule interacting to produce a synergistic effect.

Synergistic interaction between the two enantiomers of tramadol has been reported in some pain models. Because the opioid, norepinephrinergic, and serotonergic activity of tramadol reside mainly in the (+)M1 metabolite, (–)tramadol enantiomer, and (+)tramadol enantiomer, respectively, tramadol can be interpreted as a combination of three molecules, each with different pharmacological and pharmacokinetic

properties. The fortuitous combination of these molecules leads to beneficial clinical attributes of the drug.

4. Metabolic differentiation of tapentadol from tramadol

With respect to its opioid component, tramadol must undergo hepatic metabolism to (+)M1 in order to achieve significant binding affinity at MOR. This metabolism is via the cytochrome P450 system, predominantly CYP2D6, but also CYP3A4 [35]. These enzymes show a pronounced genetic polymorphism. It is thus possible that standard doses of tramadol do not always yield satisfactory analgesia in CYP2D6 polymorphic patients [36]. Furthermore, many drugs are metabolized by this same enzyme system. Thus, drug-drug interactions might occur in cases of co-medication with other drugs that are metabolized by, or inhibit, this enzyme [37].

In the case of tapentadol, both mechanisms of action (MOR agonism and NRI) reside within the parent molecule. The metabolism of tapentadol is mainly via direct glucuronidation (Phase II metabolism) to the non-analgesic tapentadol-*O*-glucuronide. Glucuronidation is mediated via a number of different isoforms of UGT (uridine-diphosphate-glucuronyl-transferase), mainly UGT1A9, UGT2B7, and UGT1A6 (Terlinden *et al.*, unpublished observations). The expression of these enzymes shows only relatively little natural variation, and they have a high capacity and are not easily saturated [38]. Thus, the expected variability in effectiveness across a patient population is smaller, and CYP P450-based drug-drug interactions are less likely [39].

Overall, tapentadol thus has a simpler pharmacokinetic-pharmacodynamic profile than does tramadol. Moreover, tapentadol does not have any active metabolites relevant for its analgesic activity [38], avoiding variable response due to genetic variability and in metabolism [40–42].

5. Clinical efficacy

In the clinical setting, an equianalgesic ratio of approximately 5:1 for long-acting formulations of tapentadol and oxycodone has been estimated (based on individually adjusted dose) [43]. This translates to an approximate ratio of 1:1.5 to 1:4 for tapentadol to tramadol, depending on conversion rates between morphine and oxycodone, and between morphine and tramadol, in the published literature [44–46]. This roughly corresponds to the potency difference between tapentadol and tramadol seen in a range of animal pain models (see above). Hence, even assuming a conservative conversion rate of 1:2 between tapentadol and tramadol, based on the recommended maximum daily dose of 400 mg for long-acting tramadol [47], this would be expected to achieve only 40% of the analgesic effect of a maximum daily dose of long-acting tapentadol (500 mg) [48]. An intermediate daily dose of 250 mg tapentadol would correspond to 500 mg tramadol, which already exceeds the recommended tramadol daily dose.

Mechanistic and functional differentiation of tapentadol and tramadol

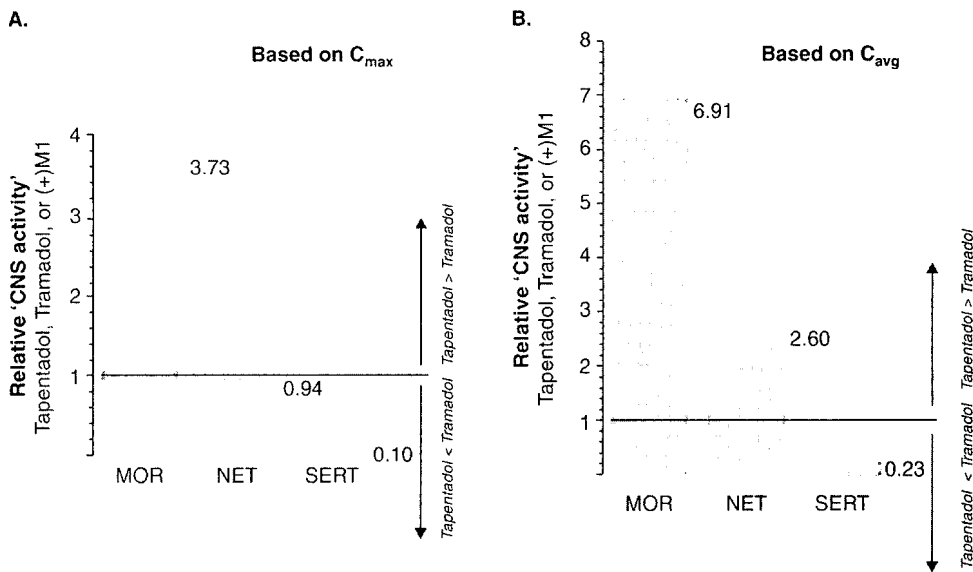


Figure 4. Comparison of the relative 'CNS Activity' (defined as the ratio of the estimated brain concentration in humans divided by the relevant functional EC₅₀ or K_i value at the receptor or monoaminergic transporter) of tapentadol and tramadol [(-) for NET and (+) for SERT] or tramadol (+)M1 metabolite (for MOR) in humans. A. C_{max}. B. C_{avg}.

Table 2. Summary of the functional differentiation of tapentadol and tramadol.

- Tapentadol is a single molecule; tramadol is a racemate
- Tapentadol has no analgesically active metabolites; tramadol has an active metabolite
- The main pathway of tapentadol metabolism is glucuronidation; tramadol is metabolized mainly via the CYP450 enzyme complex
- Tapentadol has substantially more CNS functional activity at MOR than does tramadol, about the same or more functional activity at NET, and substantially less functional activity at SERT
- The mechanisms of action of tapentadol reside in a single molecule; the mechanisms of action of tramadol reside in different molecules (enantiomers of the parent and M1 metabolite)
- Tapentadol is two to five times more potent than tramadol across a range of animal pain models. Likewise, clinically, tramadol is most effective for treating pains not requiring a strong opioid, whereas tapentadol is effective in treating pain requiring the efficacy level of strong opioids (e.g., oxycodone)
- In clinical trials, tapentadol has been shown to have comparable efficacy to oxycodone with more favorable tolerability; in usual practice, tramadol is not used for this level of pain
- Tapentadol is a schedule II drug in the United States and scheduling is in place or anticipated for all major countries where it is marketed, whereas tramadol is not scheduled in all major countries

CNS: Central nervous system; MOR: μ -opioid receptor; NET: Norepinephrine (noradrenaline) transporter.

The efficacy of tramadol is often optimized by a 'start low, go slow' approach and titration to the desired dose. However, escalating the tramadol dose in an effort to achieve the same opioid-effect as tapentadol is not a clinically viable option because: i) the dose needed would likely exceed the recommended maximum, and ii) the ratio of the brain concentration of M1 (which provides the major contribution to the opioid activity of tramadol) to the brain concentration of parent drug decreases as the oral tramadol dose is increased [9]. Further experience with a broader patient population is necessary to come to a more definite conversion rate.

A more in-depth comparison of the clinical efficacy, safety, and tolerability of tapentadol and tramadol is beyond the scope of this paper (which explicitly focuses on the chemical and

pharmacological features of the two drugs). The clinical features of tramadol have been comprehensively covered in many reviews [49-51], and there are also already some overviews of the features of tapentadol [52-54]. A direct comparison of both drugs may also be inappropriate in the present context. As outlined above, due to the different potency and efficacy, both drugs target largely different pain intensities and thus different patient populations, making a direct comparison of both drugs not feasible. In fact, the expected higher efficacy of tapentadol has led to the decision in early clinical development to use oxycodone (rather than tramadol) as the reference comparator in clinical studies. Thus, the efficacy and tolerability profile of tapentadol has largely been established based on the comparison with oxycodone, not with tramadol [55].

6. Conclusion

Tramadol and tapentadol are mechanistically and therapeutically distinct drugs although they share certain superficial chemical structural similarities (for summary, see Table 2). The pharmacological and functional differences that are observed *in vitro* and *in vivo* translate into significant clinical differences. Tramadol's somewhat complex, but fortuitous, combination of enantiomers and activemetabolite, plus pharmacokinetic profile, provides effective analgesia where a strong opioid component is not needed [56], with a low frequency of abuse [57-59]. Tapentadol's combined synergistic MOR agonism and NRI within a single molecule yields high and reliable analgesic efficacy for the treatment of pains comparable to oxycodone with more favorable gastrointestinal tolerability [60-62]. The novel features of its mechanism of action has led several authors to suggest that tapentadol should be considered in a new pharmacological class of drugs, the MOR-NRI [63-66].

7. Expert opinion

The centrally acting analgesics tapentadol and tramadol are chemically, pharmacologically, and metabolically distinct drugs. These differences in pharmacodynamic and pharmacokinetic properties—and most importantly their CNS functional activity—place them in separate classes of the category of multi-mechanistic opioid/nonopioid analgesic drugs, and result in unique and complementary options for use in different clinical situations. Tapentadol has been suggested to be a representative of a new class termed MOR-NRI. Clinical experience will determine whether this is a useful categorization for physicians trying to select the best analgesic match for a particular type of pain or for certain populations of pain patients.

Recent publications lament the lack of success of the translational research approach to drug discovery. This has been particularly true in the area of analgesic drug discovery, in which an NCE (new chemical entity) strong analgesic had not been approved in the preceding 25 years. Tapentadol demonstrates how such a targeted strategy can lead to an innovative and effective new drug. Tapentadol was built upon advances in the understanding of the basic science of pain and mechanisms of analgesia—coupled with directed medicinal chemistry modifications—to yield a new drug whose designed properties offer a differentiated clinical ('bench-to-bedside') profile.

Tramadol, a centrally acting analgesic with an established record of efficacy and safety, grew out of a discovery program designed to identify novel opioid analgesics. However, the complete picture of its mechanism of action was elucidated to a great extent after-the-fact. Its analgesic mechanisms do not reside in a single molecule, but instead in a fortuitously balanced combination of parent and metabolite molecules and each of their enantiomers. In contrast to this serendipitous combination of mechanisms, tapentadol was custom-designed to rationally combine two analgesic mechanisms (MOR

agonism and NRI) that individually and synergistically produce analgesia in models of various types of pain—within a single molecule. As part of this development, tapentadol was designed to have less serotonergic activity. The result is an innovative drug that retains the advantages of combining synergistic mechanisms of action, but with a significantly greater 'functional' opioid component and a relatively greater inhibition of the NET than of the SERT, all in a single molecule with no analgesically active metabolites. The focus on norepinephrinergic activity and the lack of relevant serotonergic activity takes into account the recent recognition that the role of serotonin in the context of pain therapy is ambivalent. While, on the one hand, serotonin functions, besides NE, as a transmitter in the descending pain inhibitory system, in contrast to NE, serotonin is also a transmitter in descending excitatory projections. Thus, in contrast to NE, serotonin not only has an anti-nociceptive effect, but can also have a pro-nociceptive effect [67,68], questioning the value of this mechanism for profound analgesic effects.

The discovery of tapentadol involved multiple steps of chemical innovations to become a unique drug. Compared to tramadol, it has a greater CNS functional activity at MOR, about the same or slightly more at NET, and substantially less at SERT. This translates into a higher potency and clinical efficacy of tapentadol compared to tramadol, despite the fact that tapentadol has a lower MOR activity than M1-tramadol, because M1-tramadol does not cross the blood-brain barrier in the same ratio as the tramadol dose is increased [9].

The two drugs thus have unique preclinical and clinical profiles appropriate for specific populations of pain patients. Tramadol offers an effective, non-scheduled (in all major countries) analgesic option that can provide pain relief for long-term use where strong opioids are not needed or desired, with low abuse potential [57-59]. Its use is optimized by titration to a dose that is compatible with use in patient populations and conditions in which the long-term use of NSAIDs, acetaminophen, or strong opioids is not desirable. The new tapentadol offers analgesia comparable to oxycodone with more favorable gastrointestinal tolerability [60-62]. The synergistic contribution of its multi-modal mechanism (MOR plus NRI) results in greater analgesic potency in a variety of preclinical models of pain, including neuropathic pain. This is also evident from the clinical dose conversion factors, for which a ratio in the range of 1:1.5 to 1:4 for tapentadol to tramadol can be estimated. Thus, with a recommended maximum daily dose of 400 mg of long-acting tramadol only 40% of the analgesic effect of a maximum daily dose (500 mg) of long-acting tapentadol can be expected (assuming a conservative conversion factor of 1:2). Already intermediate doses of tapentadol would correspond to tramadol doses exceeding the recommended daily dose, and escalation of the tramadol dose to match tapentadol's analgesic efficacy is not a viable option. Thus, the two drugs provide complementary options for a broad spectrum of types and magnitudes of

pain, giving patients more treatment options and potentially leading to better pain management.

More generally, tapentadol might serve as a template for rational drug discovery efforts in other therapeutic areas. Once the mechanistic targets that account for an existing drug's clinical utility (or disadvantages) are identified, target-directed (or off-target-avoiding) compounds can be designed and tested. By such an iterative process, the biological targets can be refined and improvements can be made, resulting in new drugs that have differentiating clinical attributes that benefit patients in different yet complementary ways. Tapentadol serves as an example both of the approach itself and of the benefits that can result from such an approach.

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Declaration of interest

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(54) **PHARMACEUTICAL COMBINATION COMPRISING 3-(3-DIMETHYLAMINO-1-ETHYL-2-METHYL-PROPYL)-PHENOL AND PARACETAMOL**

PHARMAZEUTISCHE KOMBINATION MIT 3- (3-DIMETHYLAMINO-1-ETHYL-2-METHYL-PROPYL)-PHENOL UND PARACETAMOL

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