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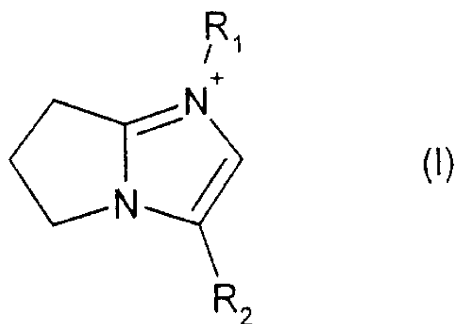
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[54] 发明名称

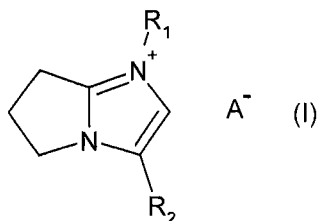
介导 CCR3 相关病症的耦合咪唑衍生物的用途

[57] 摘要

式(I)化合物在例如用于治疗 CCR3 介导病症的药物的制备中的用途。



1. 下式化合物在药物的制备中的用途



其中

R₁ 是 -未取代的(C₁₋₆)烷基或被氰基、(C₁₋₄)烷基-羰基、(C₁₋₄)烷氧基-羰基(C₁₋₂)烷基-羰基、(C₃₋₈)环烷基、硝基、卤代(C₁₋₄)烷基、卤素或杂环基单取代或者多取代的(C₁₋₆)烷基，其中杂环基有 5 或 6 个环成员和 1 至 4 个杂原子；

- (C₆₋₁₈)芳基、(C₆₋₁₈)芳基(C₁₋₆)烷基、(C₆₋₁₈)芳基-羰基(C₁₋₄)烷基、杂环基、杂环基(C₁₋₆)烷基、杂环基-羰基(C₁₋₆)烷基，其中杂环基有 5 或者 6 个环成员和 1 至 4 个选自 N、O、S 的杂原子，且其中(C₆₋₁₈)芳基或杂环基或两者任选地与未取代形式或被(C₁₋₆)烷基、(C₁₋₄)烷氧基、(C₃₋₈)环烷基、硝基、卤代(C₁₋₄)烷基或硫烷基(C₁₋₄)烷基单取代或多取代的(C₆₋₁₈)芳基或杂环基稠合；

- 未取代形式或被以下单取代或多取代的氨基羰基(C₁₋₆)烷基

(C₁₋₆)烷基；

(C₃₋₈)环烷基，

卤代(C₁₋₄)烷基，

卤素，

未取代的(C₆₋₁₈)芳基，

被(C₁₋₆)烷基、(C₁₋₄)烷氧基、(C₃₋₈)环烷基、硝基、卤代(C₁₋₄)烷

基、卤素取代的(C₆₋₁₈)芳基，

与(C₆₋₁₈)芳基或杂环基稠合的(C₆₋₁₈)芳基，其中杂环基有 5 或 6

个环成员和选自 N、O、S 的 1 至 4 个杂原子，

未取代的杂环基，其中杂环基有 5 或 6 个环成员和选自 N、O、S 的 1 至 4 个杂原子，

杂环基，其中杂环基有 5 或 6 个环成员和选自 N、O、S 的 1 至 4 个杂原子，被未取代的(C₆₋₁₈)芳基或被(C₁₋₆)烷基、(C₁₋₄)烷氧基、(C₃₋₈)环烷基、硝基、卤代(C₁₋₄)烷基、卤素取代的(C₆₋₁₈)芳基取代，

与(C₆₋₁₈)芳基或杂环基稠合的杂环基，其中杂环基有 5 或 6 个环成员和选自 N、O、S 的 1 至 4 个杂原子，

R₂ 是 -未取代的(C₆₋₁₈)芳基或被(C₁₋₄)烷基、(C₁₋₄)烷氧基、(C₁₋₄)卤代烷基或卤素取代的(C₆₋₁₈)芳基；且

A⁻ 是药物可接受的阴离子。

2. 权利要求 1 的用途，其中在式(I)化合物中(C₆₋₁₈)芳基是苯基、任选地与苯基或杂环基稠合，其中杂环基有 5 或 6 个环成员和 1 至 4 个选自 N、O、S 的杂原子。

3. 权利要求 1 或 2 的用途，其中在式(I)化合物中

R₁ 是(C₁₋₄)烷基、氰基(C₁₋₄)烷基、(C₁₋₂)烷基-羰基(C₁₋₂)烷基、(C₁₋₄)烷氧基-羰基-(C₁₋₂)烷基-羰基(C₁₋₂)烷基、

未取代的苯基或被(C₁₋₄)烷基、(C₁₋₂)烷氧基、卤素、硝基单取代或多取代的苯基；

未取代的苯基(C₁₋₄)烷基或被(C₁₋₄)烷基、(C₁₋₂)烷氧基、硝基一次或多次取代的苯基(C₁₋₄)烷基；

未取代的苯基-羰基(C₁₋₂)烷基或被(C₁₋₄)烷基、(C₁₋₂)烷氧基、卤素、硝基、(C₃₋₈)环烷基、(C₁₋₄)烷基-硫烷基单取代或多取代的苯基-羰基(C₁₋₂)烷基，

杂环基-(C₁₋₄)烷基，其中杂环基有 5 或 6 个环成员和 1 至 2 个选自 N、S 的杂原子，任选地与苯基稠合；

杂环基-羰基(C₁₋₄)烷基,其中杂环基有5或6个环成员和1至2个选自N、S的杂原子,任选地与苯基稠合;

未取代的氨基-羰基(C₁₋₂)烷基或被(C₁₋₄)烷基一次或多次取代的氨基-羰基(C₁₋₂)烷基、未取代的或取代的(C₆₋₁₈)芳基、未取代的或取代的苯基(C₁₋₂)烷基、(C₃₋₆)环烷基,未取代的或取代的杂环基,其中杂环基有5或6个环成员和1至2个选自N、S的杂原子,任选地与苯基稠合;

R₂ 是未取代的苯基或被(C₁₋₄)烷基、(C₁₋₄)烷氧基或卤素取代的苯基,
A⁻ 如权利要求1所定义。

4. 式(I)化合物在制备治疗由CCR3介导的病症的药物中的用途,其中

R₁ 是 -未取代的(C₁₋₆)烷基或被氰基、(C₁₋₄)烷基-羰基、(C₁₋₄)烷氧基-羰基(C₁₋₂)烷基-羰基、(C₃₋₈)环烷基、硝基、卤代(C₁₋₄)烷基、卤素或杂环基单取代或者多取代的(C₁₋₆)烷基,其中杂环基有5或6个环成员和1至4个杂原子;

- (C₆₋₁₈)芳基、(C₆₋₁₈)芳基(C₁₋₆)烷基、(C₆₋₁₈)芳基-羰基(C₁₋₄)烷基、杂环基、杂环基(C₁₋₆)烷基、杂环基-羰基(C₁₋₆)烷基,其中杂环基有5或者6个环成员和1至4个选自N、O、S的杂原子,且其中(C₆₋₁₈)芳基或杂环基或两者任选地与未取代形式或被(C₁₋₆)烷基、(C₁₋₄)烷氧基、(C₃₋₈)环烷基、硝基、卤代(C₁₋₄)烷基、卤素或硫烷基(C₁₋₄)烷基单取代或多取代的(C₆₋₁₈)芳基或杂环基稠合;

- 未取代形式或被以下单取代或多取代的氨基羰基(C₁₋₆)烷基
(C₁₋₆)烷基;

(C₃₋₈)环烷基,

卤代(C₁₋₄)烷基,

卤素,

未取代的(C₆₋₁₈)芳基,

被(C₁₋₆)烷基、(C₁₋₄)烷氧基、(C₃₋₈)环烷基、硝基、卤代(C₁₋₄)烷基、
卤素取代的(C₆₋₁₈)芳基,

与(C₆₋₁₈)芳基或杂环基稠合的(C₆₋₁₈)芳基, 其中杂环基有 5 或 6 个环成员和选自 N、O、S 的 1 至 4 个杂原子,

未取代的杂环基, 其中杂环基有 5 或 6 个环成员和选自 N、O、S 的 1 至 4 个杂原子,

杂环基, 其中杂环基有 5 或 6 个环成员和选自 N、O、S 的 1 至 4 个杂原子, 被未取代的(C₆₋₁₈)芳基或被(C₁₋₆)烷基、(C₁₋₄)烷氧基、(C₃₋₈)环烷基、硝基、卤代(C₁₋₄)烷基、卤素取代的(C₆₋₁₈)芳基取代,

与(C₆₋₁₈)芳基或杂环基稠合的杂环基, 其中杂环基有 5 或 6 个环成员和选自 N、O、S 的 1 至 4 个杂原子,

R₂ 是 -未取代的(C₆₋₁₈)芳基或被(C₁₋₄)烷基、(C₁₋₄)烷氧基、(C₁₋₄)卤代烷基或卤素取代的(C₆₋₁₈)芳基;

A⁻ 是药物可接受的阴离子。

5. 权利要求 4 的用途, 其中在式(I)的化合物中

R₁ 是(C₁₋₄)烷基、氰基(C₁₋₄)烷基、(C₁₋₂)烷基-羰基(C₁₋₂)烷基、(C₁₋₄)烷氧基-羰基-(C₁₋₂)烷基-羰基(C₁₋₂)烷基、

未取代的苯基或被(C₁₋₄)烷基、(C₁₋₂)烷氧基、卤素、硝基单取代或多取代的苯基;

未取代的苯基(C₁₋₄)烷基, 或被(C₁₋₄)烷基、(C₁₋₂)烷氧基、卤素、硝基一次或多次取代的苯基(C₁₋₄)烷基;

未取代的苯基-羰基(C₁₋₂)烷基或被(C₁₋₄)烷基、(C₁₋₂)烷氧基、卤素、硝基、(C₃₋₈)环烷基、(C₁₋₄)烷基-硫烷基单取代或多取代的苯基-羰基(C₁₋₂)烷基,

杂环基-(C₁₋₄)烷基, 其中杂环基有 5 或 6 个环成员和 1 至 2 个选自 N、S 的杂原子, 任选地与苯基稠合;

杂环基-羰基(C₁₋₄)烷基, 其中杂环基有 5 或 6 个环成员和 1 至 2 个选自 N、S 的杂原子, 任选地与苯基稠合;

未取代的氨基-羰基(C₁₋₂)烷基或被(C₁₋₄)烷基、未取代的或取代的(C₆₋₁₈)芳基、未取代的或取代的苯基(C₁₋₂)烷基、(C₃₋₆)环烷基，未取代的或取代的杂环基一次或多次取代的氨基-羰基(C₁₋₂)烷基，其中杂环基有 5 或 6 个环成员和 1 至 2 个选自 N、S 的杂原子，任选地与苯基稠合。

R₂ 是未取代的苯基或被(C₁₋₄)烷基、(C₁₋₄)烷氧基或卤素取代的苯基，
A⁻ 如权利要求 5 所定义。

6. 权利要求 4 或 5 中任意一项的用途，其中所述的由 CCR3 介导的病症是炎性或过敏性病症，特别是炎性或阻塞性气道疾病。

7. 由 CCR3 介导的疾病的治疗方法，所述的治疗包括给需要这类治疗的个体施用有效量的权利要求 1 至 5 的任意一项的式(I)化合物。

8. 权利要求 7 的治疗方法，其中所述的疾病是炎性或过敏性疾病，特别是炎性或阻塞性气道疾病。

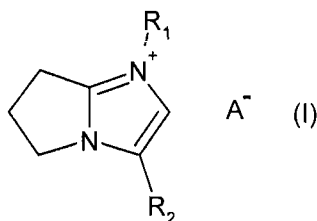
9. 权利要求 7 或 8 中任意一项的方法，其中权利要求 1 至 5 的任意一项的式(I)化合物与另一种药物活性剂同时或依次地联合施用。

10. 药物组合物，其包含权利要求 1 至 5 的任意一项的式(I)化合物和至少一种药物赋形剂。

11. 权利要求 10 的药物组合物，还包含另一种药物活性剂。

介导 CCR3 相关病症的稠合咪唑衍生物的用途

本发明涉及有机化合物、例如指定式的化合物在药物制备中的用途。
在一个方面，本发明提供了在药物的制备中的下式化合物



其中

- R_1 是 -未取代的(C_{1-6})烷基或被氰基、(C_{1-4})烷基-羰基、(C_{1-4})烷氧基-羰基、(C_{1-2})烷基-羰基、(C_{3-8})环烷基、硝基、卤代(C_{1-4})烷基、卤素或杂环基单取代或者多取代的(C_{1-6})烷基，其中杂环基有 5 或 6 个环成员和 1 至 4 个杂原子；
- (C_{6-18})芳基、(C_{6-18})芳基(C_{1-6})烷基、(C_{6-18})芳基-羰基(C_{1-4})烷基、杂环基、杂环基(C_{1-6})烷基、杂环基-羰基(C_{1-6})烷基，其中杂环基有 5 或者 6 个环成员和 1 至 4 个选自 N、O、S 的杂原子，且其中(C_{6-18})芳基或杂环基或两者任选地与未取代形式或被(C_{1-6})烷基、(C_{1-4})烷氧基、(C_{3-8})环烷基、硝基、卤代(C_{1-4})烷基或硫烷基(C_{1-4})烷基单取代或多取代的(C_{6-18})芳基或杂环基稠合；
 - 未取代形式或被以下单取代或多取代的氨基羰基(C_{1-6})烷基
(C_{1-6})烷基；
(C_{3-8})环烷基，
卤代(C_{1-4})烷基，
卤素，
未取代的(C_{6-18})芳基，
被(C_{1-6})烷基、(C_{1-4})烷氧基、(C_{3-8})环烷基、硝基、卤代(C_{1-4})烷基、

卤素取代的(C₆₋₁₈)芳基,

与(C₆₋₁₈)芳基或杂环基稠合的(C₆₋₁₈)芳基, 其中杂环基有 5 或 6 个环成员和选自 N、O、S 的 1 至 4 个杂原子,

未取代的杂环基, 其中杂环基有 5 或 6 个环成员和选自 N、O、S 的 1 至 4 个杂原子,

杂环基, 其中杂环基有 5 或 6 个环成员和选自 N、O、S 的 1 至 4 个杂原子, 被未取代的(C₆₋₁₈)芳基或被(C₁₋₆)烷基、(C₁₋₄)烷氧基、(C₃₋₈)环烷基、硝基、卤代(C₁₋₄)烷基、卤素取代的(C₆₋₁₈)芳基取代,

与(C₆₋₁₈)芳基或杂环基稠合的杂环基, 其中杂环基有 5 或 6 个环成员和选自 N、O、S 的 1 至 4 个杂原子,

R₂ 是 -未取代的(C₆₋₁₈)芳基或被(C₁₋₄)烷基、(C₁₋₄)烷氧基、(C₁₋₄)卤代烷基或卤素取代的(C₆₋₁₈)芳基; 且

A⁻ 是药物可接受的阴离子。

在一方面, 本发明提供了在药物的制备中的式(I)化合物, 其中

R₁ 是 -未取代的(C₁₋₆)烷基或被氰基、(C₁₋₄)烷基-羰基、(C₁₋₄)烷氧基-羰基、(C₁₋₂)烷基-羰基、(C₃₋₈)环烷基、硝基、卤代(C₁₋₄)烷基、卤素或杂环基单取代或多取代的(C₁₋₆)烷基, 其中杂环基有 5 或 6 个环成员和 1 至 4 个杂原子;

- (C₆₋₁₈)芳基、(C₆₋₁₈)芳基-羰基(C₁₋₄)烷基、杂环基、杂环基(C₁₋₆)烷基、杂环基-羰基(C₁₋₆)烷基, 其中杂环基有 5 或 6 个环成员和选自 N、O、S 的 1 至 4 个杂原子, 且其中(C₆₋₁₈)芳基或杂环基或两者任选地与未取代形式或被(C₁₋₆)烷基、(C₁₋₄)烷氧基、(C₃₋₈)环烷基、硝基、卤代(C₁₋₄)烷基、硫烷基(C₁₋₄)烷基或卤素单取代或多取代的(C₆₋₁₈)芳基或杂环基稠合;
- 未取代形式或被以下单取代或多取代的氨基羰基(C₁₋₆)烷基(C₁₋₆)烷基;
(C₃₋₈)环烷基,

卤代(C₁₋₄)烷基,
卤素,
未取代的(C₆₋₁₈)芳基,
被(C₁₋₆)烷基、(C₁₋₄)烷氧基、(C₃₋₈)环烷基、硝基取代的(C₆₋₁₈)芳基,
卤代(C₁₋₄)烷基、卤素,
与(C₆₋₁₈)芳基或杂环基稠合的(C₆₋₁₈)芳基, 其中杂环基有 5 或 6 个环成员和 1 至 4 个选自 N、O、S 的杂原子,
未取代的杂环基, 其中杂环基有 5 或 6 个环成员和 1 至 4 个选自 N、O、S 的杂原子,
杂环基, 其中杂环基有 5 或 6 个环成员和 1 至 4 个选自 N、O、S 的杂原子, 被未取代的(C₆₋₁₈)芳基或被(C₁₋₆)烷基、(C₁₋₄)烷氧基、(C₃₋₈)环烷基、硝基、卤代(C₁₋₄)烷基、卤素取代的(C₆₋₁₈)芳基取代,
与(C₆₋₁₈)芳基或杂环基稠合的杂环基, 其中杂环基有 5 或 6 个环成员和 1 至 4 个选自 N、O、S 的杂原子,
R₂ 和 A 如上文的定义。

在另一方面本发明提供了式(I)化合物, 其中(C₆₋₁₈)芳基是苯基、任选地与苯基或杂环基稠合, 其中杂环基有 5 或 6 个环成员和 1 至 4 个选自 N、O、S 的杂原子。

在另一方面本发明提供了式(I)化合物, 其中
R₁ 是(C₁₋₄)烷基、氰基(C₁₋₄)烷基、(C₁₋₂)烷基-羰基(C₁₋₂)烷基、(C₁₋₄)烷氧基-羰基-(C₁₋₂)烷基-羰基(C₁₋₂)烷基、未取代的苯基或被(C₁₋₄)烷基、(C₁₋₂)烷氧基、卤素、硝基单取代或多取代的苯基; 未取代的苯基(C₁₋₄)烷基或被(C₁₋₄)烷基、(C₁₋₂)烷氧基、硝基单取代或多取代的苯基(C₁₋₄)烷基; 未取代的苯基-羰基(C₁₋₂)烷基或被(C₁₋₄)烷基、(C₁₋₂)烷氧基、卤素、硝基、(C₃₋₈)环烷基、(C₁₋₄)烷基-硫烷基单取代或多取代的苯基-羰基(C₁₋₂)烷基, 杂环基-(C₁₋₄)烷基, 其中杂环基有 5 或 6 个环成员和 1 至 2 个选

自 N、S 的杂原子，任选地与苯基稠合；

杂环基-羰基(C₁₋₄)烷基，其中杂环基有 5 或 6 个环成员和 1 至 2 个选自 N、S 的杂原子，任选地与苯基稠合；

未取代的氨基-羰基(C₁₋₂)烷基或被(C₁₋₄)烷基单取代或多取代的氨基-羰基(C₁₋₂)烷基，未取代的或取代的(C₆₋₁₈)芳基，未取代的或取代的苯基(C₁₋₂)烷基、(C₃₋₆)环烷基、未取代的或取代的杂环基，其中杂环基有 5 或 6 个环成员和 1 至 2 个选自 N、S 的杂原子，任选地与苯基稠合。

R₂ 是未取代的苯基或被(C₁₋₄)烷基、(C₁₋₄)烷氧基或卤素取代的苯基，

A⁻ 如上文的定义。

在另一方面本发明提供了式(I)化合物，其中

R₁ 是(C₁₋₄)烷基、氰基(C₁₋₄)烷基、(C₁₋₂)烷基-羰基(C₁₋₂)烷基、(C₁₋₄)烷氧基-羰基-(C₁₋₂)烷基-羰基(C₁₋₂)烷基、未取代的苯基或被(C₁₋₄)烷基、(C₁₋₂)烷氧基、卤素、硝基单取代或多取代的苯基；未取代的苯基(C₁₋₄)烷基，未取代的苯基-羰基(C₁₋₂)烷基或被(C₁₋₄)烷基、(C₁₋₂)烷氧基、卤素、硝基、(C₃₋₈)环烷基、(C₁₋₄)烷基-硫烷基单取代或多取代的苯基-羰基(C₁₋₂)烷基，杂环基-(C₁₋₄)烷基，其中杂环基有 5 或 6 个环成员和 1 至 2 个选自 N、S 的杂原子，任选地与苯基稠合；

杂环基-羰基(C₁₋₄)烷基，其中杂环基有 5 或 6 个环成员和 1 至 2 个选自 N、S 的杂原子，任选地与苯基稠合；

未取代的氨基-羰基(C₁₋₂)烷基或被(C₁₋₄)烷基、未取代的或取代的(C₆₋₁₈)芳基、未取代的或取代的苯基(C₁₋₂)烷基、(C₃₋₆)环烷基，未取代的或取代的杂环基，其中杂环基有 5 或 6 个环成员和 1 至 2 个选自 N、S 的杂原子，任选地与苯基稠合。

R₂ 是未取代的苯基或被(C₁₋₄)烷基、(C₁₋₄)烷氧基或卤素取代的苯基，

A⁻ 如上文的定义。

如果本文不是另外定义

- 烷基包括(C₁₋₈)烷基, 例如(C₁₋₆)烷基, 诸如例如(C₁₋₄)烷基;
- 烷氧基包括(C₁₋₈)烷氧基, 例如(C₁₋₆)烷氧基, 诸如例如(C₁₋₄)烷氧基;
- (C₃₋₈)环烷基包括例如(C₃₋₆)环烷基; 诸如例如环己基;
- 芳基包括(C₆₋₁₈)芳基, 例如苯基; 任选地与(C₆₋₁₈)芳基、例如苯基或者与杂环基、例如有 6 个环成员和 2 个 O 的杂原子的杂环基稠合, 诸如例如二噁英;
- 杂环基包括有 1 至 4 个选自 S、O 和 N 的杂原子例如 N、S 的 5 或 6 元环; 诸如例如噻吩或噻唑;
任选地与另一个环(体系)稠合, 例如与一个或多个(C₆₋₁₈)芳基例如苯基凑合, 或与杂环基稠合;
- 卤素包括氟、氯、溴;
- 卤代烷基包括卤代(C₁₋₄)烷基, 其中卤素是一个或多个卤素, 优选三氟甲基;

任何基团可以是未取代的或取代的, 例如被有机化学中传统的基团取代, 例如包括选自卤素、卤代烷基、烷基羰基氧基、烷氧基、羟基、氨基、烷基羰基氨基、氨基烷基羰基氨基、羟基烷基氨基、氨基烷基氨基、烷基氨基、二烷基氨基、有 5 或 6 个环成员和 1 至 4 个选自 N、O、S 的杂原子的杂环基; (C₁₋₄)烷基杂环基, 其中杂环基有 5 或 6 个环成员和 1 至 4 个选自 N、O、S 的杂原子; 羟基(C₁₋₄)烷基杂环基, 其中杂环基有 5 或 6 个环成员和 1 至 4 个选自 N、O、S 的杂原子; 羧基、(C₁₋₄)烷基羰基氧基、氨基(C₁₋₄)-烷基羰基氧基。

在式 I 化合物中, 每个单独定义的取代基可以是优选的取代基, 例如彼此独立定义的取代基。

在另一方面, 本发明提供了式(I)化合物, 条件是排除实施例 1 至 378 的化合物。

本发明使用的或提供的化合物是下文中定义的“(根据)本发明的化

合物”。本发明的化合物包括化合物的盐的形式、溶剂合物的形式和盐及溶剂合物的形式。

本发明的化合物是以盐的形式存在的。

这些盐优选地包括药物可接受的盐，尽管包括药物不可接受的盐，例如用于制备/分离/纯化的目的。

阴离子 A^- 是药物可接受的阴离子，诸如是来自无机酸的，例如氢卤酸诸如氢氟酸、盐酸、氢溴酸或氢碘酸、硝酸、硫酸、磷酸；和来自有机酸的，例如脂肪族单羧酸诸如甲酸、乙酸、三氟乙酸、丙酸和丁酸，脂肪族羟基酸诸如乳酸、枸橼酸、酒石酸或苹果酸；二羧酸诸如马来酸或琥珀酸，芳香族羧酸诸如苯甲酸、对-氯苯甲酸、二苯基乙酸或三苯基乙酸、芳香族羟基酸诸如邻-羟基苯甲酸、对-羟基苯甲酸、1-羟基萘-2-甲酸或 3-羟基萘-2-甲酸、和磺酸诸如甲磺酸或苯磺酸。

优选地 A^- 是卤素，例如溴和氯，最优选地是氯。

本发明的化合物的盐形式和溶剂合物的形式可被转化为非溶剂合物形式的盐形式的相应化合物；反之亦然。

本发明的化合物可以纯异构体形式或其混合物形式存在，例如光学异构体、非对映异构体、顺/反异构体。本发明的化合物可包括例如不对称碳原子并因此可存在对映异构体或非对映异构体及其混合物的形式，例如外消旋体。任何不对称碳原子可以(R)-、(S)-或(R,S)-构象，优选地以(R)-或(S)-构象存在。

异构体混合物可以用适当的方法分离，例如根据传统方法、例如与传统方法相似的方法获得纯异构体。本发明包括任何异构体形式和任何异构体混合物存在的化合物。

本发明亦包括式 I 化合物的互变异构体，其中互变异构体可存在。

本发明的化合物例如包括式 I 化合物，显示药理活性并因此用作药物。例如，式 I 化合物用于制备治疗受 CCR3 介导病症的药物。

在另一方面，本发明提供了用于制备治疗受 CCR3 介导病症的药物的

式(I)化合物, 其中

R_1 是-未取代的(C_{1-6})烷基或被氰基、(C_{1-4})烷基-羰基、(C_{1-4})烷氧基-羰基(C_{1-2})

烷基-羰基、(C_{3-8})环烷基、硝基、卤代(C_{1-4})烷基、卤素或杂环基单取代或多取代的(C_{1-6})烷基, 其中杂环基有 5 或 6 个环成员和 1 至 4 个杂原子;

- (C_{6-18})芳基、(C_{6-18})芳基(C_{1-6})烷基、(C_{6-18})芳基-羰基(C_{1-4})烷基、杂环基、杂环基(C_{1-6})烷基、杂环基-羰基(C_{1-6})烷基, 其中杂环基有 5 或 6 个环成员和 1 至 4 个选自 N、O、S 的杂原子且其中(C_{6-18})芳基或杂环基或二者任选地与未取代的形式或被(C_{1-6})烷基、(C_{1-4})烷氧基、(C_{3-8})环烷基、硝基、卤代(C_{1-4})烷基、卤素或硫烷基(C_{1-4})烷基单取代或多取代的(C_{6-18})芳基或杂环基稠合;

-未取代形式的或被以下单取代或多取代的氨基羰基(C_{1-6})烷基
(C_{1-6})烷基;

(C_{3-8})环烷基,

卤代(C_{1-4})烷基,

卤素,

未取代的(C_{6-18})芳基,

被(C_{1-6})烷基、(C_{1-4})烷氧基、(C_{3-8})环烷基、硝基、卤代(C_{1-4})烷基、

卤素取代的(C_{6-18})芳基,

与(C_{6-18})芳基或杂环基稠合的(C_{6-18})芳基, 其中杂环基有 5 或 6 个环成员和 1 至 4 个选自 N、O、S 的杂原子,

未取代的杂环基, 其中杂环基有 5 或 6 个环成员和 1 至 4 个选自 N、O、S 的杂原子,

杂环基, 其中杂环基有 5 或 6 个环成员和 1 至 4 个选自 N、O、S 的杂原子, 被未取代的(C_{6-18})芳基或被(C_{1-6})烷基、(C_{1-4})烷氧基、(C_{3-8})环烷基、硝基、卤代(C_{1-4})烷基、卤素取代的(C_{6-18})芳基所取代,

与(C_{6-18})芳基或杂环基稠合的杂环基, 其中杂环基有 5 或 6 个环成员和 1 至 4 个选自 N、O、S 的杂原子,

R_2 是 - 未取代的(C₆₋₁₈)芳基或被(C₁₋₄)烷基、(C₁₋₄)烷氧基、(C₁₋₄)卤代烷基或卤素取代的(C₆₋₁₈)芳基;

A^- 是药物可接受的阴离子。

在另一方面,本发明提供了用于制备治疗受 CCR3 介导的病症的药物的式(I)化合物, 其中

R_1 是(C₁₋₄)烷基、氰基(C₁₋₄)烷基、(C₁₋₂)烷基-羰基(C₁₋₂)烷基、(C₁₋₄)烷氧基-羰基-(C₁₋₂)烷基-羰基(C₁₋₂)烷基,

未取代的苯基或被(C₁₋₄)烷基、(C₁₋₂)烷氧基、卤素、硝基单取代或多取代的苯基;

未取代的苯基(C₁₋₄)烷基或被(C₁₋₄)烷基、(C₁₋₂)烷氧基、卤素、硝基单取代或多取代苯基(C₁₋₄)烷基;

未取代的苯基-羰基(C₁₋₂)烷基或被(C₁₋₄)烷基、(C₁₋₂)烷氧基、卤素、硝基、(C₃₋₈)环烷基、(C₁₋₄)烷基-硫烷基、杂环基-(C₁₋₄)烷基单取代或多取代的苯基-羰基(C₁₋₂)烷基, 其中杂环基有 5 或 6 个环成员和 1 至 2 个选自 N、S 的杂原子, 任选地与苯基稠合;

杂环基-羰基(C₁₋₄)烷基, 其中杂环基有 5 或 6 个环成员和 1 至 2 个选自 N、S 的杂原子, 任选地与苯基稠合;

未取代的氨基-羰基(C₁₋₂)烷基或被(C₁₋₄)烷基、未取代的或取代的(C₆₋₁₈)芳基、未取代的或取代的苯基(C₁₋₂)烷基、(C₃₋₆)环烷基、未取代的或取代的杂环基单取代或多取代的氨基-羰基(C₁₋₂)烷基, 其中杂环基有 5 或 6 个环成员和 1 至 2 个选自 N、S 的杂原子, 任选地与苯基稠合;

R_2 是未取代的苯基或被(C₁₋₄)烷基、(C₁₋₄)烷氧基或卤素取代的苯基, 且 A^- 是如上文所定义的。

本发明的化合物起 CCR3 受体拮抗剂的作用, 由此抑制炎症细胞、特别是嗜酸性粒细胞的浸润和活化并抑制过敏反应。本发明化合物的抑制性质可以在下列试验中得到证实:

在本试验中测定本发明的化合物对人嗜酸性粒细胞趋化因子与人

CCR3 结合的影响。表达人 CCR3 的重组细胞通过在细胞表面 WGA 与糖蛋白的碳水化合物残基间的特异性相互作用,被麦芽凝集素(WGA)聚乙烯基甲苯胺(PVT)SPA 珠(购自 Amersham)捕获。 $[^{125}\text{I}]$ -人嗜酸性粒细胞趋化因子(购自 Amersham)特异性结合 CCR3 受体,使 $[^{125}\text{I}]$ -人嗜酸性粒细胞趋化因子与 SPA 珠非常接近。 $[^{125}\text{I}]$ -人嗜酸性粒细胞趋化因子发射的 α 粒子可以通过接近激发珠中的荧光团使其产生光。溶液中游离的 $[^{125}\text{I}]$ -人嗜酸性粒细胞趋化因子与闪烁体距离较远而不产生光。因此闪烁计数是衡量被试验化合物抑制嗜酸性粒细胞趋化因子与 CCR3 结合程度的指标。

测定缓冲液的制备:将 5.96 g HEPES 和 7.0 g 氯化钠溶解于蒸馏水中,加入 1 M CaCl_2 水溶液(1 mL)和 1 M MgCl_2 水溶液(5 mL)。用 NaOH 调节 pH 值至 7.6,用蒸馏水调节使溶液的终体积为 1 L。然后,将 5 g 牛血清白蛋白和 0.1 g 叠氮化钠溶于溶液中,配置好的缓冲液放置 4℃ 贮存。在使用的当天,向每 50 mL 缓冲液中加入 COMPLETE™ 蛋白酶抑制剂混合物药片(购自 Boehringer)。

匀浆缓冲液的制备:将 Tris-碱(2.42 g)溶解于蒸馏水中,用盐酸将溶液 pH 调节至 7.6,将溶液用蒸馏水稀释成终体积为 1 L。将配置好的缓冲液放置 4℃ 贮存。在使用的当天,向每 50 mL 缓冲液中加入 COMPLETE™ 蛋白酶抑制剂混合物药片。

膜的制备:将稳定表达 CCR3 的融合鼠嗜碱细胞白血病(RBL-2H3)细胞应用无酶的细胞分裂缓冲液从组织培养瓶中分离出来,再悬浮于磷酸缓冲盐中,将细胞离心(800 g, 5 分钟),离心后的沉淀重新悬浮于冰冻的匀浆缓冲液中,每克细胞应用 1 mL 该缓冲液,在冰上孵育 30 分钟。细胞在冰上用玻璃研钵和杵研磨 10 次进行匀浆化。将匀浆进行离心(800 g, 5 分钟, 4℃),上清液继续离心(48,000 g, 30 分钟, 4℃),沉淀再次溶解于含有 10%(v/v)甘油的匀浆缓冲液中。膜制剂的蛋白含量采用布拉德福方法(Anal. Biochem. (1976)72: 248)进行估计,将各等份立即冷冻并贮存于 -80℃。

本测定方法在每孔终体积为 250 μL 的 Optiplate™ 微孔板(购自 Canberra Packard)中完成。在选择的微孔板的孔中加入 50 μL 待测化合物

的含有 5%DMSO 的测定缓冲液溶液(浓度从 0.01 nM 到 10 μ M)。将 50 μ L 含有 5%DMSO 的测定缓冲液加入到其他选择孔中以确定总结合量。将 50 μ L 100 nM 的人嗜酸性粒细胞趋化因子(购自 R&D Systems)的含有 5%DMSO 的测定缓冲液溶液加入到其他选择孔中以确定非特异性结合量。每个孔中均加入 50 μ L 浓度为 250 pM 的溶解于含有 5%DMSO 的测定缓冲液的 [^{125} I]-人嗜酸性粒细胞趋化因子(购自 Amersham)溶液(使其终浓度为每孔 50 pM), 50 μ L 溶于测定缓冲液的 WGA-PVT SPA 珠(使其终浓度为每孔 1.0 mg 珠)和 100 μ L 浓度为 100 μ g 蛋白溶解于测定缓冲液(使其终浓度为每孔 10 μ g 蛋白)的膜制剂。该板在室温下孵育 4 小时, 然后用 TopSeal-STM密封带(购自 Canberra Packard)按照生产商的说明将其密封。应用 Canberra Packard TopCountTM 闪烁计数器计数其闪烁量, 每孔计数 1 分钟。应用常规方法, 由浓度抑制曲线确定产生 50%抑制(IC₅₀)时待测化合物的浓度。

下文实施例中的化合物在上述试验中具有 1 μ M 或低于 1 μ M 的 IC₅₀ 值。例如, 实施例 241 化合物的 IC₅₀ 值为 6nM, 实施例 322 化合物的 IC₅₀ 值为 21nM, 实施例 341 化合物的 IC₅₀ 值为 23nM。

相对于对 α -1 肾上腺素受体结合的抑制而言, 实施例中的大多数化合物对抑制 CCR3 结合显示出选择性。

本发明的化合物对 α -1 肾上腺素受体结合的抑制性质可以通过下列试验证实:

将得自雄性 Sprague-Dawley 大鼠(175-200g)的脑皮质切开并用玻璃/特氟纶匀化器在 10 份冰冷的 0.32M 蔗糖(含有 1mM MgCl₂ 二水合物和 1mM K₂HPO₄)中匀化。细胞膜于 1000 $\times$ g 离心分离 15 分钟, 除去沉淀, 重复离心分离。合并上清液, 于 18,000 $\times$ g 离心分离 15 分钟。沉淀用 10 份水进行渗透压休克, 并置于冰上 30 分钟。于 39,000 $\times$ g 离心分离悬浮液 20 分钟, 再悬浮于含有 20 mM Tris 的 Krebs-Henseleit 缓冲液 pH 7.4(1.17mM 无水 MgSO₄, 4.69 mM KCl, 0.7 mM 无水 K₂HPO₄, 0.11 M NaCl, 11 mM D-葡萄糖和 25 mM NaHCO₃)中, 并于 -20 $^{\circ}$ C 放置 2 日。然后于 20-23 $^{\circ}$ C 融溶细胞膜, 通过 18,000 $\times$ g 离心 15 分钟用 Krebs-Henseleit 缓冲液洗涤 3 次,

于 4℃放置过夜，然后再洗涤 3 次。将最终的沉淀用玻璃/特氟纶匀化器再以 125ml/100 细胞膜的悬浮于相同缓冲液中。取样本测定蛋白质浓度(采用 Bradford 测定法，以 γ 球蛋白作为标准)，剩余各份存放于 -80℃待用。

得到的细胞膜进行放射配体结合测定分析。该测定以一式三份进行，采用含有 [^{125} I]-HEAT(Amersham)(40 pM, K_d : 58.9 ± 18.7 pM)、未标记的待测化合物和细胞膜(57.1 μ g/ml)的 96 孔板进行，终体积 250 μ l(测定缓冲液含有 50 mM Tris 碱和 0.9% (w/v) NaCl, pH 7.4)。于 37℃温育板 60 分钟后，经 Whatman™ GF/C 96 孔板过滤器快速真空过滤。每板采用 Brandel 细胞捕获器(Gaithersburg, MD)，用 10ml 冰冷的测定缓冲液洗涤 3 次。随后于 50℃，将板干燥 3 小时。向每孔中加入 40 μ l Microscint 20，于室温下再温育板 20 分钟，在 Packard TopCount NXT™闪烁计数器上进行残留放射活性定量分析。

先将待测化合物的储备液溶于 100%DMSO，并用测定缓冲液稀释至所需浓度，DMSO 的浓度为 1%(v/v)。采用常规方法，根据浓度-抑制曲线测定产生 50%抑制作用时的待测化合物的浓度(IC₅₀)。

考虑到本发明化合物对 CCR3 结合的抑制作用，本发明的化合物可以用于治疗由 CCR3 介导的病症，特别是炎性或过敏性病症。根据本发明的治疗可以是对症治疗或预防性治疗。

因此，本发明的化合物可应用于治疗炎性或阻塞性气道疾病，例如能够减少组织损伤、支气管高反应性、改变疾病进程。本发明可应用于治疗炎性或阻塞性气道疾病，包括各种类型或起源的哮喘，包括内源性(非过敏性)哮喘和外源性(过敏性)哮喘、轻度哮喘、中度哮喘、重度哮喘、支气管哮喘、运动诱导性哮喘、职业性哮喘和细菌感染诱导的哮喘。哮喘的治疗也被理解为包括对所有治疗对象的治疗，如小于 4 或 5 岁的患者，这些患者出现喘息症状并被确诊或可能被诊断为“婴儿喘鸣”，这是医学界重点关注的一类病人，并且现在被确诊为初始或早期哮喘阶段。(为方便起见，该类具体的哮喘病症被称为“婴儿喘鸣综合征”。)

对于哮喘的预防功能可以通过减少该病发生频率或如急性哮喘或支气管收缩发作的剧烈程度、改善肺部功能或改善气道高反应性来证明。它可

以进一步通过减少对其它症状性治疗的需要来证明,如治疗或有目的地限制或当症状发生时将其中止的治疗,例如采用抗炎药(如皮质甾类)或支气管扩张药。哮喘预防的益处特别是在“早晨发作”(morning dipping)的对象中更加显而易见。“早晨发作”是一种确诊的哮喘综合征,在很大比例的哮喘患者中普遍存在,其特点是哮喘通常在远离前次症状性哮喘治疗的时间段发作,例如,在早晨约4-6点。

本发明可以应用的其它的炎性或阻塞性气道疾病或病症包括急性肺损伤(ALI)、急性/成人呼吸窘迫综合征(ARDS)、慢性肺阻塞、气道或肺部疾病(COPD、COAD 或 COLD),包括慢性支气管炎或与之相关的呼吸困难、肺气肿以及其他药物特别是吸入药物治疗引起的气道高反应性的恶化。本发明也应用于治疗各种类型或起源的支气管炎,包括急性、花生仁吸入性、卡他性、格鲁布性、慢性或结核性支气管炎。本发明可以应用的另外的炎性或阻塞性气道疾病包括各种类型和起源的尘肺(一种炎性、通常为职业性肺部疾病,通常伴随有气道阻塞,无论是慢性还是急性,并且由重复性吸入粉尘引起),如铝质沉着病、炭末沉着症、石棉沉着症、石末沉着病、鸵鸟毛尘肺、肺铁末沉着症、硅肺病、烟末沉着病和棉屑沉着病。

考虑到其抗炎活性,特别是与抑制嗜酸性粒细胞活化有关的抗炎活性,本发明化合物也应用于治疗嗜酸性粒细胞相关障碍,如嗜酸性粒细胞增多,特别是气道嗜酸性粒细胞相关障碍(如涉及肺部组织的病态嗜酸性粒细胞浸润),包括高嗜酸性粒细胞增多症,因为它们可以影响气道和/或肺,并且还包括例如吕弗勒综合征引发或伴随气道的嗜酸性粒细胞相关性障碍、嗜酸性粒细胞肺炎、寄生物(特别是后生动物)的侵染(包括热带嗜酸性粒细胞增多)、支气管肺部曲霉病、结节性多动脉炎(包括丘-施综合征)、嗜酸性粒细胞肉芽肿和药物反应影响气道而产生的嗜酸性粒细胞相关障碍。

本发明化合物也可以用于治疗炎性或过敏性皮肤病症,例如银屑病、接触性皮炎、特应性皮炎、斑秃、多形性红斑、疱疹样皮炎、硬皮病、白癜风、过敏性脉管炎、荨麻疹、大疱性类天疱疮、红斑狼疮、天疱疮、获得性大疱样表皮松解以及其它炎性或过敏性皮肤病症。

本发明化合物也可以用于治疗其它疾病或病症,特别是含有炎性成分

的疾病或病症，例如治疗：眼部疾病或病症(如结膜炎、干燥性角结膜炎和春季结膜炎)，影响鼻腔的疾病(包括过敏性鼻炎例如特应性、慢性或季节性鼻炎)，以及胃肠道炎性病症(例如炎性肠病，如溃疡性结肠炎及克罗恩病)，包括类风湿性关节炎、牛皮癣性关节炎、强直性脊柱炎和全身性硬化症的骨及关节疾病，及诸如囊性纤维化、肺动脉高血压、动脉粥样硬化、多发性硬化症、糖尿病(I型)、重症肌无力、高IgE综合征及急性和慢性同种异体移植物排斥，例如心脏、肾脏、肝脏、肺脏或骨髓移植后的其他疾病。

本发明化合物在抑制炎症病症、例如炎症呼吸道疾病中的有效性可以在气道炎症或其它炎性病症的动物模型、例如小鼠或大鼠模型中得到证明，例如以下文献所述：Szarka 等人, *J. Immunol. Methods* (1997) 202: 49-57; Renzi 等人, *Am. Rev. Respir. Dis.* (1993) 148: 932-939; Tsuyuki 等人, *J. Clin. Invest.* (1995) 96: 2924-2931 和 Cernadas 等人(1999) *Am. J. Respir. Cell Mol. Biol.* 20: 1-8。

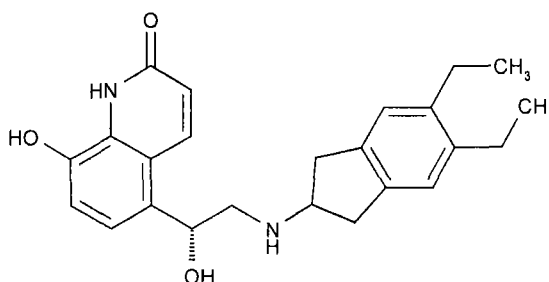
本发明化合物也可以用作联合治疗剂，与其它药物物质(例如抗炎、支气管扩张、抗组胺或镇咳药物物质)联合使用，特别是治疗阻塞性或炎性气道疾病，例如在上文中上述的那些疾病，例如，它可以作为此类药物的治疗活性的增效剂或者作为降低此类药物的所需剂量或可能存在的副作用的手段。本发明化合物可以在固定的药物组合物中与其它药物混和，或者可以在其它药物物质施用之前、同时或之后分别施用。

此类抗炎药物包括类固醇，特别是糖皮质类固醇例如布地奈德、倍氯米松(beclamethasone)、氟替卡松、环索奈德或莫米松，或者在 WO 02/88167、WO 02/12266、WO 02/100879、WO 04/039827 或 WO 02/00679(特别是实施例 3、11、14、17、19、26、34、37、39、51、60、67、72、73、90、99 和 101 的化合物)中描述的一类固醇类；LTB₄拮抗剂例如在 US 5451700 中描述的那些，以及 LY293111、CGS025019C、CP-195543、SC-53228、BIIL 284、ONO 4057 和 SB 209247；LTD₄拮抗剂，如孟鲁司特、扎鲁司特；多巴胺受体激动剂，如卡麦角林、溴隐亭、罗匹尼罗和 4-羟基-7-[2-[[2-[[3-(2-苯基乙氧基)丙基]磺酰基]乙基]-氨基]乙基]-2(3H)-苯并噻唑

酮及其可药用盐(盐酸盐为 Viozan[®] - AstraZeneca); PDE4 抑制剂, 如西洛司特 (Ariflo[®] GSK)、罗氟司特 (Byk Gulden)、V-11294A(Napp)、BAY19-8004(Bayer)、SCH-351591(Schering-Plough)、阿罗茶碱(Almirall Prodesfarma)、PD189659/PD168787(Parke-Davis)、AWD-12-281(Asta Medica)、CDC-801(Celgene)、SelCID(TM)CC-10004 (Celgene)、VM554/UM565(Vernalis)、T-440(Tanabe)、KW-4490(Kyowa Hakko Kogyo), 以及在 WO 92/19594、WO 93/19749、WO 93/19750、WO 93/19751、WO 99/16766、WO 01/13953、WO 03/104204、WO 03/104205、WO 04/000814、WO 04/000839、WO 04/005258、WO 04/018450、WO 04/018451、WO 04/018457、WO 04/018465、WO 04/018431、WO 04/018449、WO 04/018450、WO 04/018451、WO 04/018457、WO 04/018465、WO 04/019944、WO 04/019945、WO 04/045607 和 WO 04/037805 以及在 WO 98/18796 和 WO 03/39544 中公开的那些; A2a 激动剂, 如在 EP 409595A2、EP 1052264、EP 1241176、WO 94/17090、WO 96/02543、WO 96/02553、WO 98/28319、WO 99/24449、WO 99/24450、WO 99/24451、WO 99/38877、WO 99/41267、WO 99/67263、WO 99/67264、WO 99/67265、WO 99/67266、WO 00/23457、WO 00/77018、WO 00/78774、WO 01/23399、WO 01/27130、WO 01/27131、WO 01/60835、WO 01/94368、WO 02/00676、WO 02/22630、WO 02/96462、WO 03/086408、WO 04/039762、WO 04/039766、WO 04/045618、WO 04/046083 中描述的那些; 和 A2b 拮抗剂, 如在 WO 02/42298 中描述的那些。

此类支气管扩张药物包括抗胆碱能药物或抗毒蕈碱药物, 特别是异丙托溴铵、氧托溴铵、噻托溴铵盐和 CHF 4226(Chiesi), 和格隆溴铵, 还有那些在 WO 01/04118、WO 02/51841、WO 02/53564、WO 03/00840、WO 03/87094、WO 04/05285、WO 02/00652、WO 03/53966、EP 424021、US 5171744、US 3714357、US 5171744、WO 03/33495 和 WO 04/018422 中描述的药物; 以及 β -2 肾上腺素能受体激动剂, 如沙丁胺醇、异丙喘宁、特布他林、沙美特罗、非诺特罗、丙卡特罗, 特别是福莫特罗和其可药用盐, WO 0075114 的式(I)化合物(游离或盐或溶剂化物形式), 该文献并入本文中

作参考, 优选该文献实施例中的化合物, 特别是下式化合物



及其可药用盐以及 WO 04/16601 的式(I)化合物(游离或盐或溶剂化物形式), 更多的适宜的 β -2-肾上腺受体激动剂包括例如在 JP 05025045、US 2002/0055651、WO 93/18007、WO 99/64035、WO 01/42193、WO 01/83462、WO 02/066422、WO 02/070490、WO 02/076933、WO 03/24439、WO 03/72539、WO 03/42160、WO 03/91204、WO 03/42164、WO 03/99764、WO 04/11416、WO 04/16578、WO 04/22547、WO 04/32921、WO 04/33412、WO 04/37773、WO 04/37807、WO 04/39762、WO 04/39766、WO 04/45618 和 WO 04/46083 中描述的那些化合物。

联合治疗的抗组胺药物物质包括盐酸西替利嗪、对乙酰氨基酚、富马酸氯马斯汀、异丙嗪、氯雷他定、地氯雷他定、苯海拉明和盐酸非索非那定、activastine、阿司咪唑、氮革斯汀、依巴斯汀、依匹斯汀、咪唑斯汀和特芬那定, 以及在 JP 2004107299、WO 03/99807 和 WO 04/26841 中公开的那些。

本发明的化合物与一种或多种类固醇、 β -2 激动剂、PDE4 抑制剂或 LTD4 拮抗剂的组合可以用于治疗例如 COPD 或特别是哮喘。本发明化合物与抗胆碱能药物或抗毒蕈碱药物、PDE4 抑制剂、多巴胺受体激动剂或 LTB4 拮抗剂的组合可以应用于治疗如哮喘或特别是 COPD。

本发明的化合物与抗炎药物的其他有用的组合是与其他趋化因子受体拮抗剂的组合, 如 CCR1、CCR2、CCR4、CCR5、CCR6、CCR7、CCR8、CCR9 和 CCR10、CXCR1、CXCR2、CXCR3、CXCR4、CXCR5, 特别是 CCR5 拮抗剂, 如 Schering-Plough 拮抗剂 SC-351125、SCH-55700 和 SCH-D, Takeda 拮抗剂如氯化 N-[[4-[[[6,7-二氢-2-(4-甲基苯基)-5H-苯并环庚烯-8-基]羰基]氨基]苯基]-甲基]四氢-N,N-二甲基-2H-吡喃-4-铵

(TAK-770), CCR5 拮抗剂在 US 6166037(特别是权利要求 18 和 19)、WO 00/66558(特别是权利要求 8)和 WO 00/66559(特别是权利要求 9)、WO 04/018425 和 WO 04/026873 中描述。

根据上述,本发明也提供了用于治疗 CCR3 介导的病症的方法,例如炎性或过敏性病症,特别是炎性或阻塞性气道疾病,该方法包括给需要的个体、特别是人类个体施用有效量的前面所描述的游离形式或可药用盐形式的式(I)化合物。

另一方面,本发明提供如前面所定义的游离或可药用盐形式的式(I)化合物在生产治疗 CCR3 介导的疾病的药物中的用途,所述疾病例如炎性或过敏性病症,特别是炎性或阻塞性气道疾病。

本发明的化合物可以通过适当的途径施用,如口服施用,例如以片剂或胶囊剂的形式;非肠道施用,如静脉注射;吸入施用,例如治疗炎性或阻塞性气道疾病;鼻内施用,如治疗过敏性鼻炎;局部皮肤施用,如治疗特应性皮炎;或直肠施用,如治疗炎性肠病。

另一方面,本发明也提供药物组合物,该药物组合物包括游离形式或可药用盐形式的式 I 化合物作为活性成分和任意的可药用的稀释剂或载体。该组合物还可以包含联合治疗药物,如前面所描述的一种抗炎支气管扩张药物或抗组胺药物。该组合物可以应用常规的稀释剂或赋形剂和已知的制药技术制备。因此,口服剂型可以包括片剂和胶囊剂。局部施用的制剂可以为乳膏剂、软膏剂、凝胶剂或经皮给药系统、如贴剂的形式。吸入施用的组合物可以包括气雾剂或其它雾化或干粉制剂。

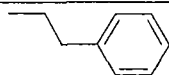
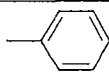
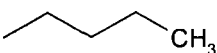
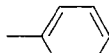
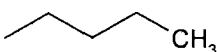
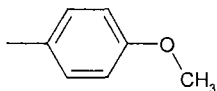
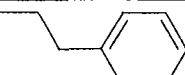
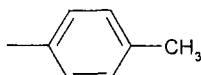
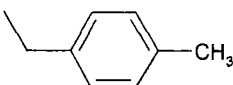
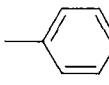
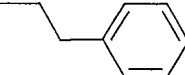
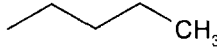
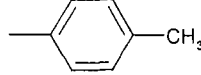
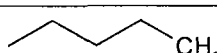
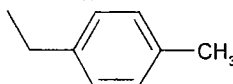
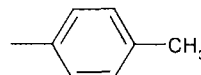
当组合物包含气雾剂制剂时,优选其中包含例如氢-氟-烷(HFA)抛射剂,如 HFA134a 或 HFA227 或它们的混合物,并且还可以包含一种或多种本领域已知的助溶剂,如乙醇(至多 20%(重量)),和/或一种或多种表面活性剂,如油酸或脱水山梨糖醇三油酸酯,和/或一种或多种填充剂,如乳糖。当组合物包含干粉制剂时,优选该组合物包含颗粒直径至多 10 微米的式(I)化合物,任选含有用于所需的颗粒分布的稀释剂或载体,例如乳糖,以及防止产物由于潮湿而引起性能变差的化合物,如硬脂酸镁。当组合物包含雾化制剂时,优选其中包含如式(I)化合物或者溶解或者悬浮在溶媒中,

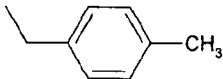
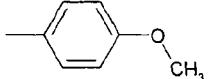
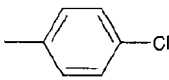
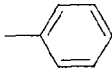
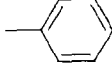
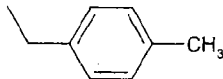
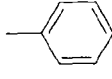
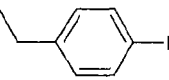
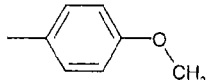
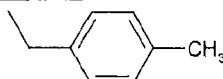
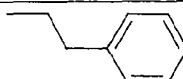
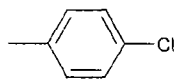
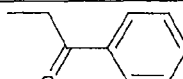
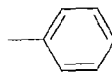
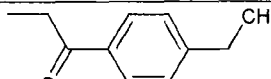
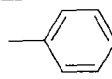
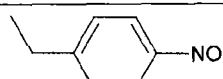
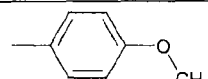
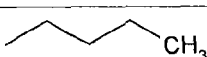
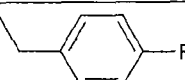
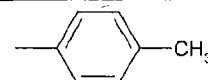
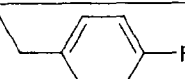
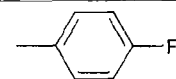
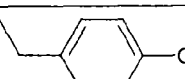
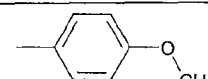
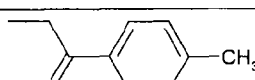
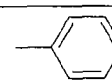
所述溶媒含有水、如乙醇或丙二醇的助溶剂以及可以为表面活性剂的稳定剂。

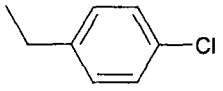
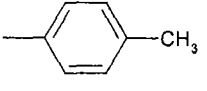
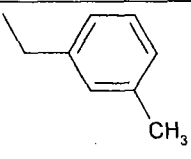
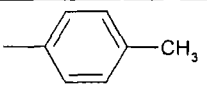
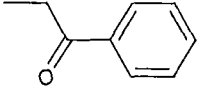
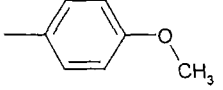
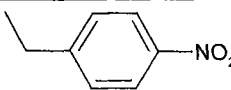
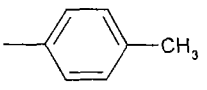
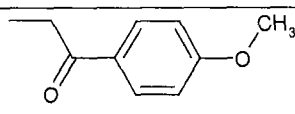
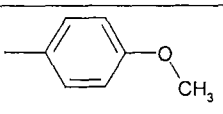
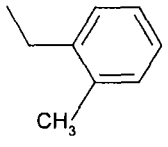
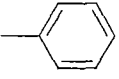
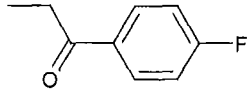
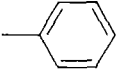
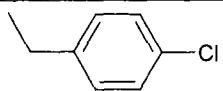
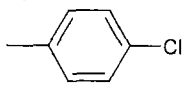
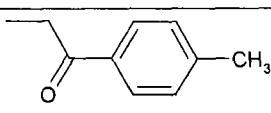
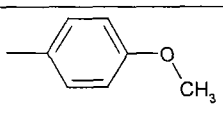
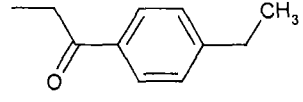
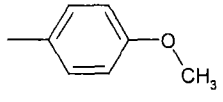
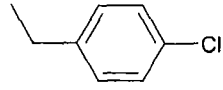
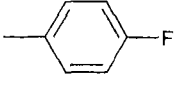
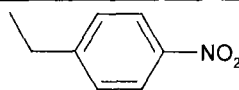
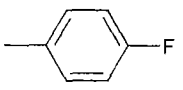
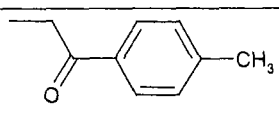
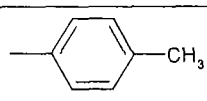
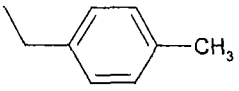
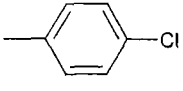
本发明包括(A)吸入形式的本发明的化合物,如气雾剂或其它雾化组合物,或者可吸入粒子如微粉化形式的本发明的化合物;(B)包含吸入形式的本发明的化合物的吸入药物;(C)包括吸入形式的本发明的化合物及吸入装置的药用产品;和(D)包含吸入形式的本发明的化合物的吸入装置。

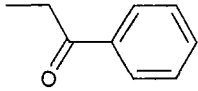
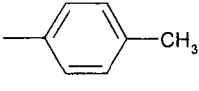
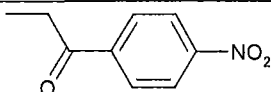
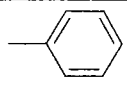
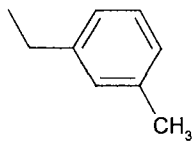
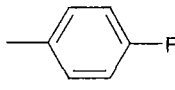
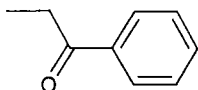
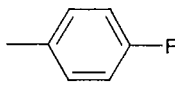
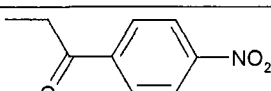
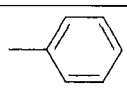
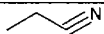
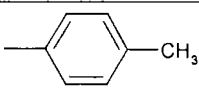
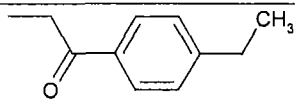
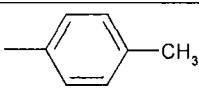
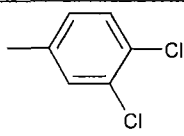
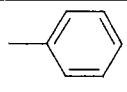
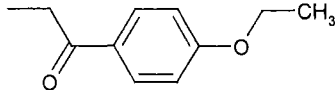
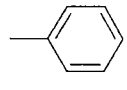
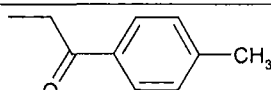
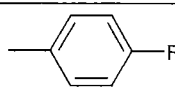
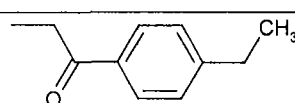
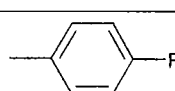
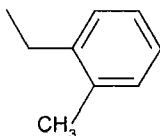
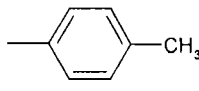
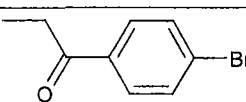
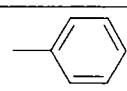
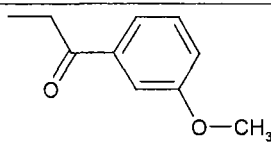
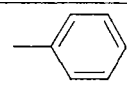
当然,在实施本发明时采用的本发明的药物的剂量应当根据例如所治疗的病症、所需的效果以及施用途径的不同而不同。通常而言,吸入施用的适宜的日剂量为 0.01-30 mg/kg,而口服施用的适宜的日剂量为 0.01-100 mg/kg。

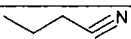
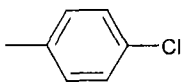
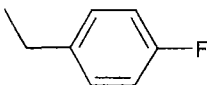
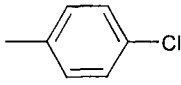
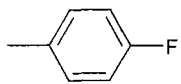
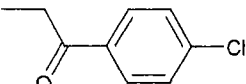
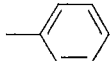
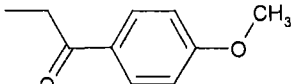
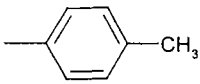
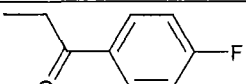
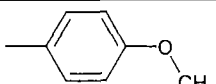
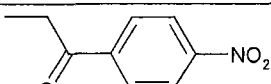
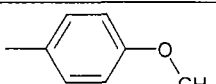
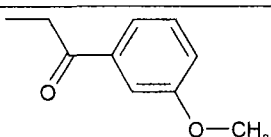
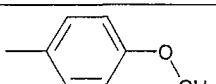
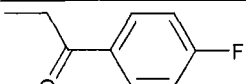
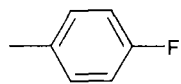
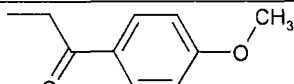
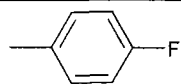
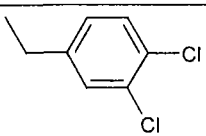
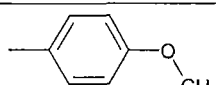
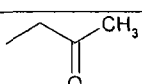
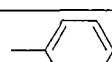
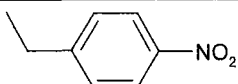
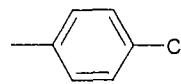
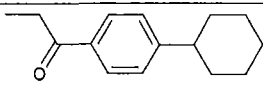
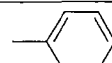
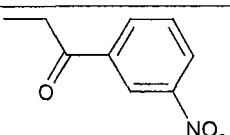
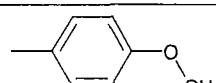
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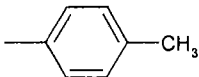
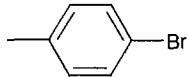
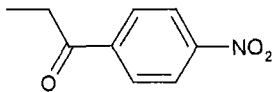
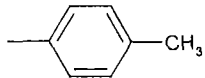
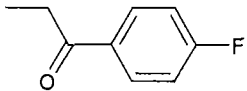
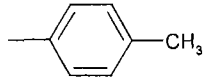
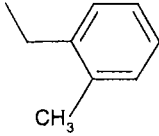
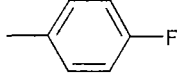
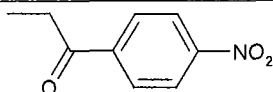
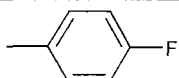
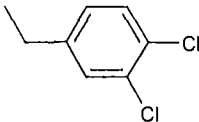
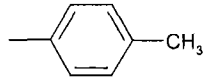
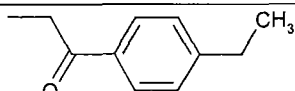
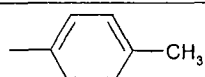
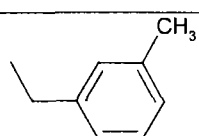
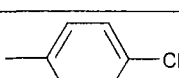
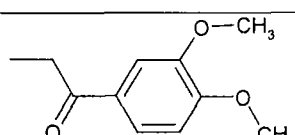
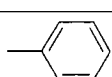
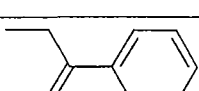
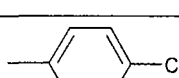
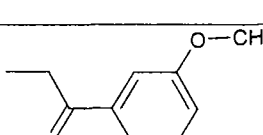
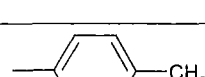
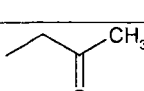
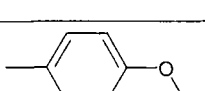
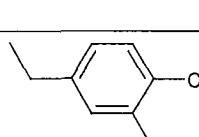
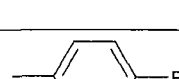
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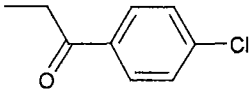
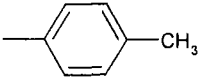
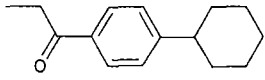
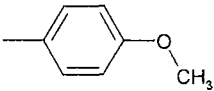
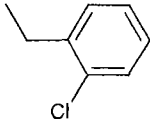
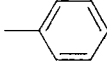
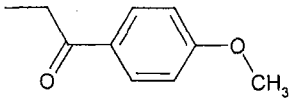
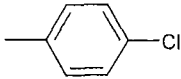
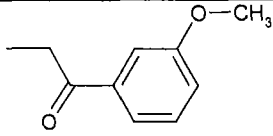
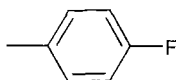
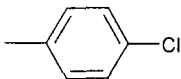
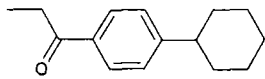
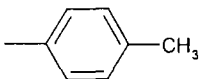
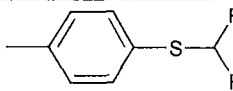
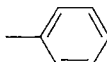
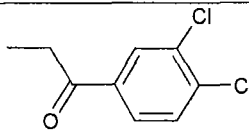
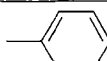
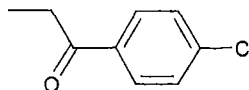
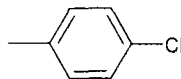
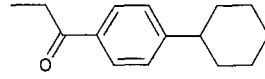
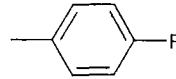
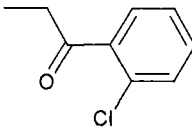
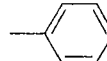
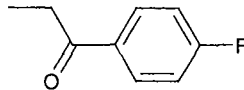
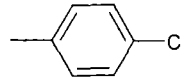
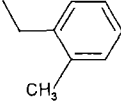
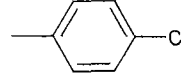
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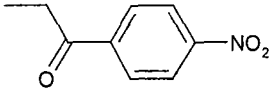
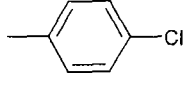
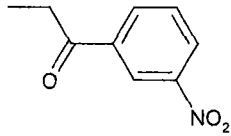
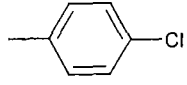
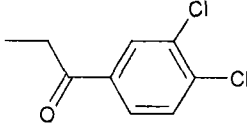
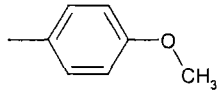
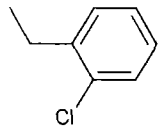
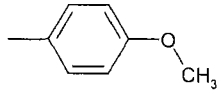
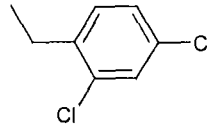
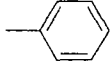
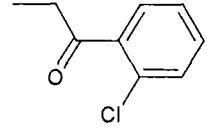
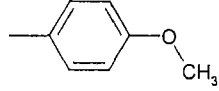
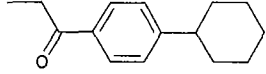
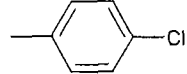
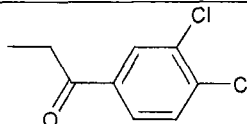
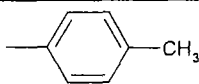
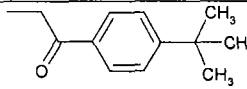
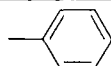
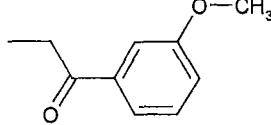
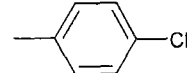
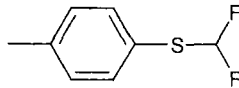
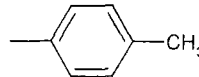
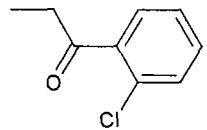
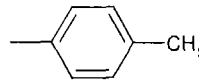
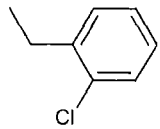
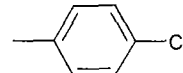
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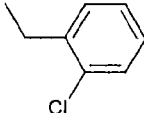
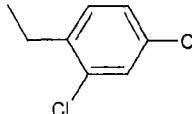
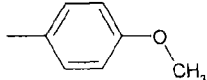
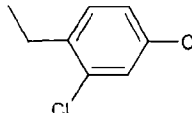
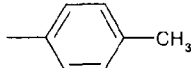
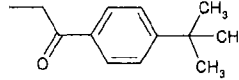
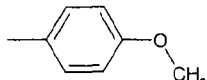
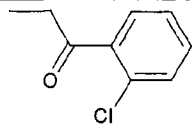
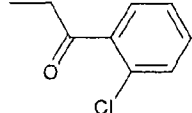
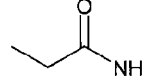
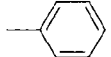
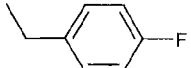
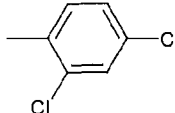
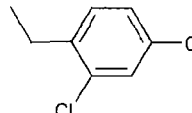
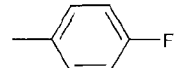
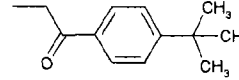
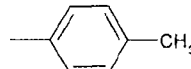
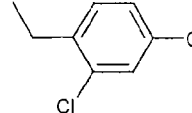
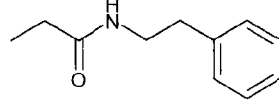
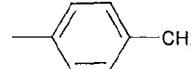
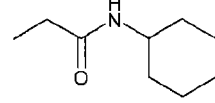
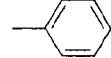
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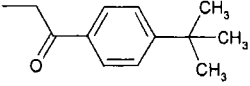
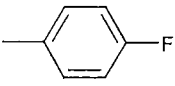
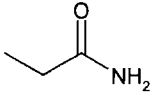
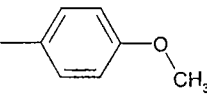
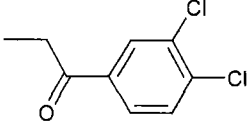
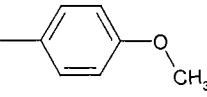
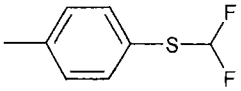
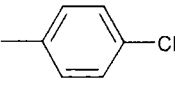
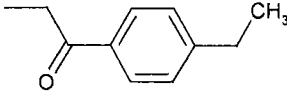
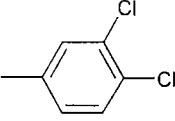
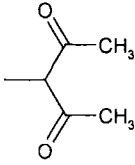
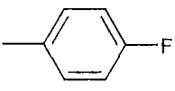
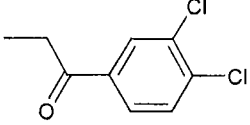
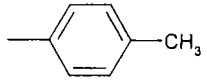
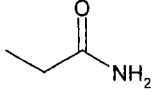
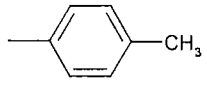
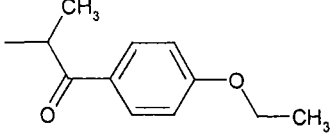
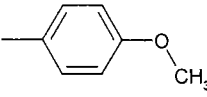
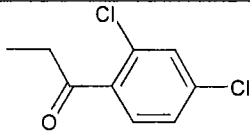
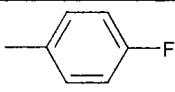
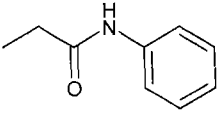
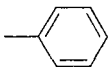
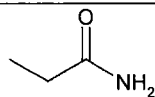
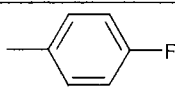
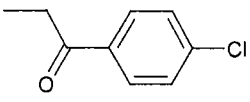
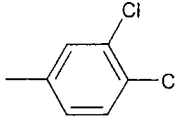
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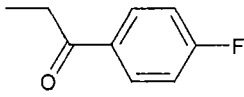
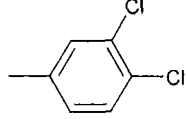
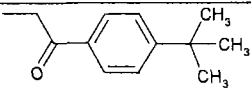
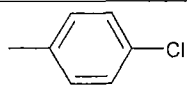
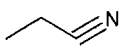
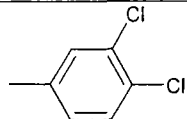
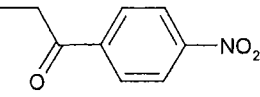
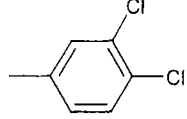
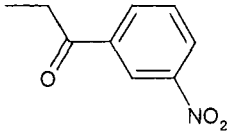
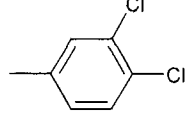
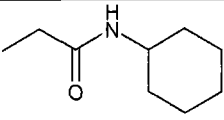
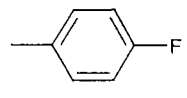
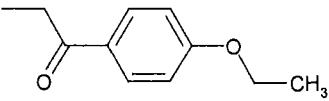
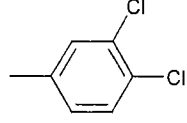
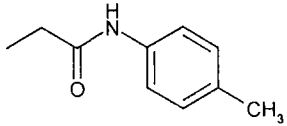
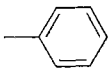
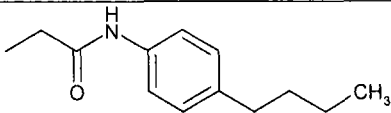
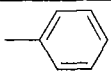
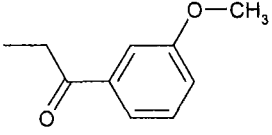
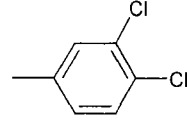
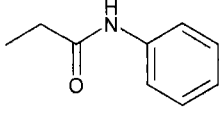
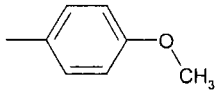
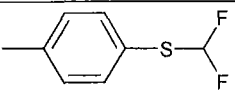
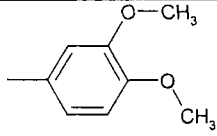
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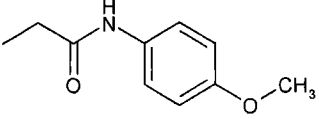
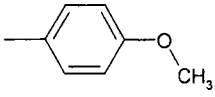
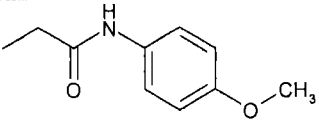
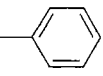
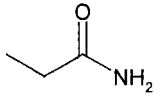
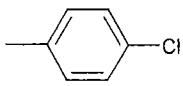
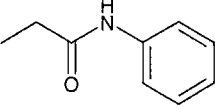
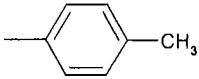
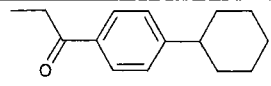
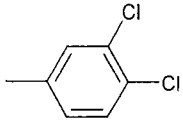
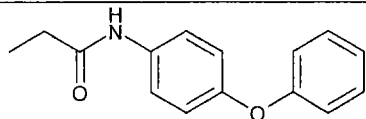
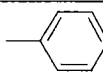
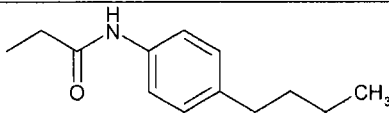
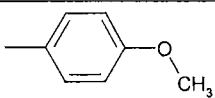
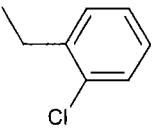
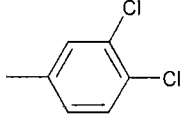
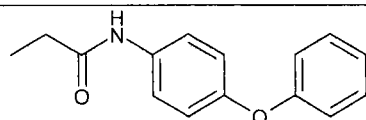
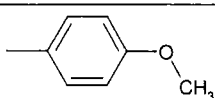
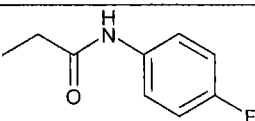
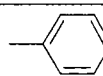
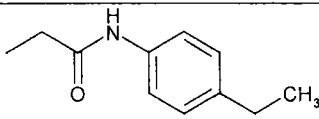
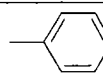
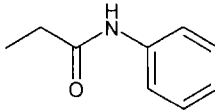
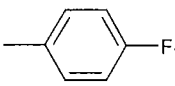
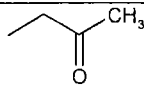
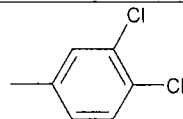
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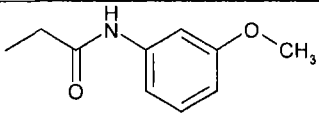
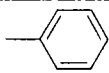
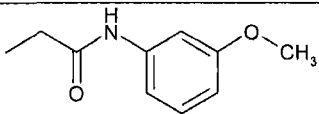
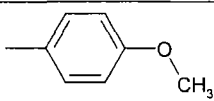
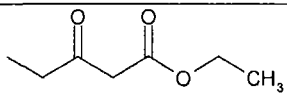
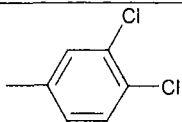
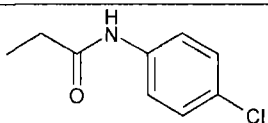
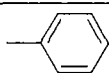
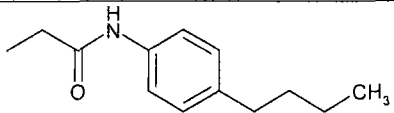
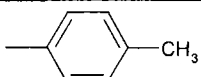
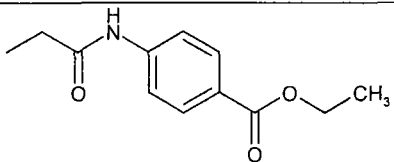
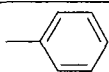
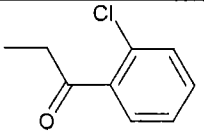
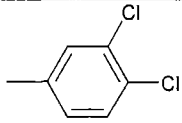
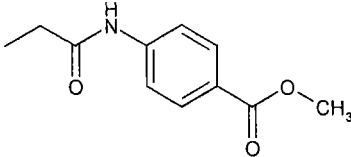
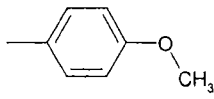
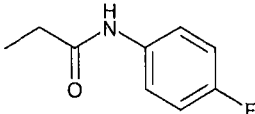
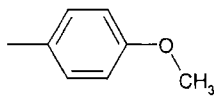
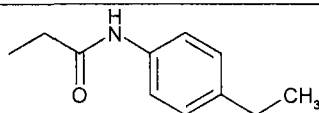
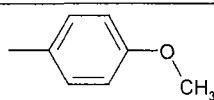
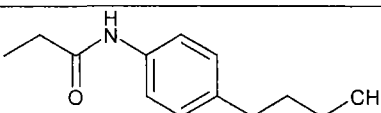
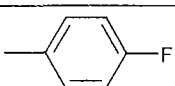
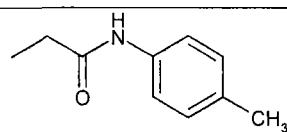
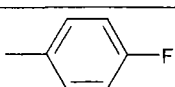
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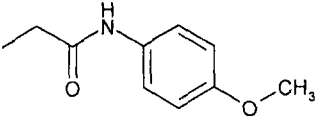
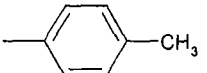
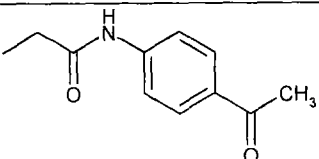
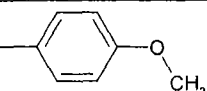
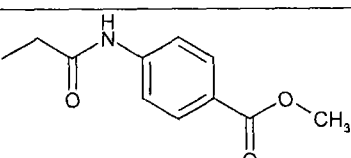
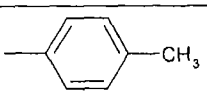
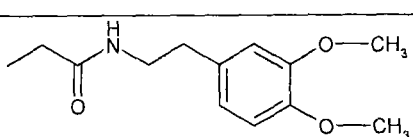
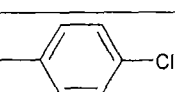
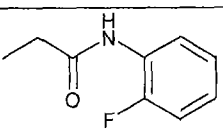
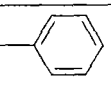
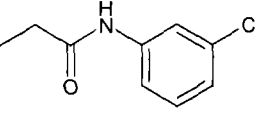
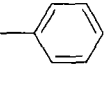
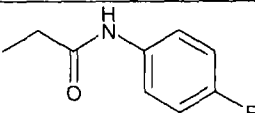
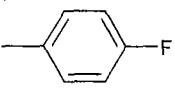
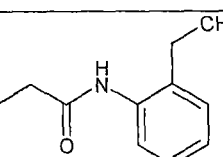
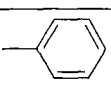
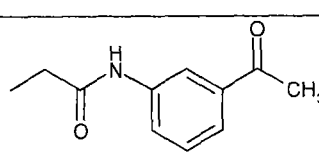
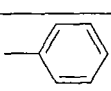
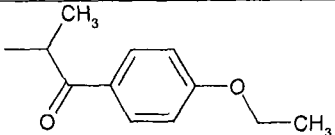
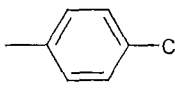
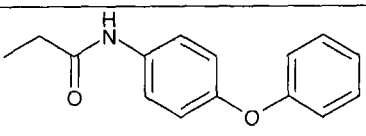
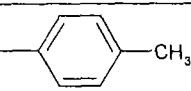
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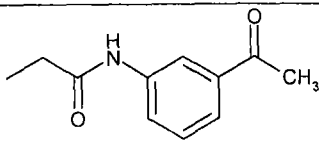
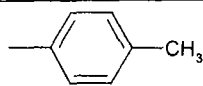
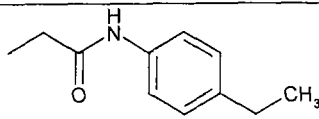
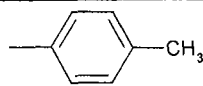
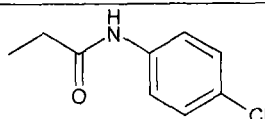
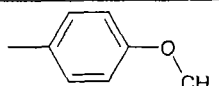
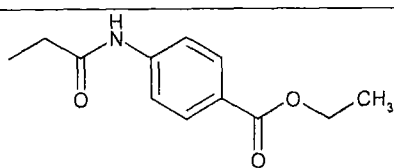
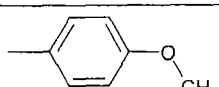
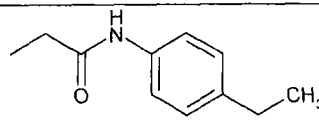
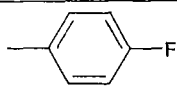
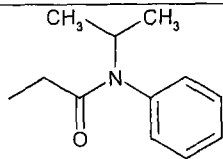
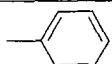
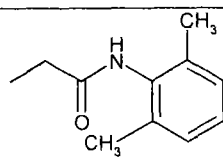
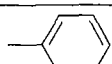
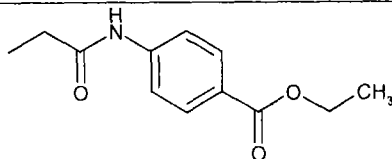
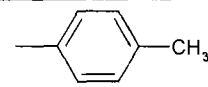
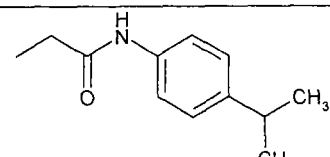
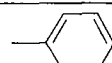
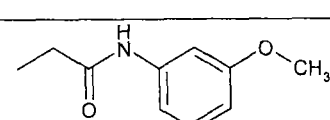
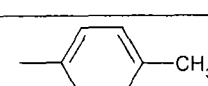
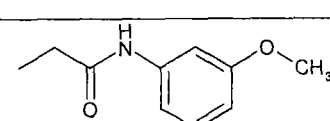
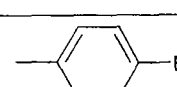
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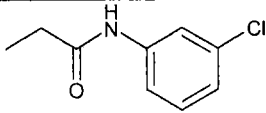
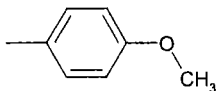
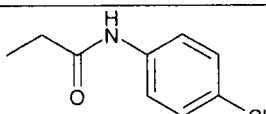
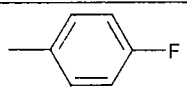
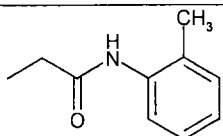
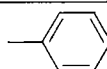
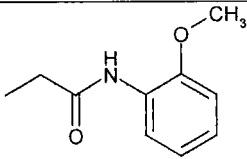
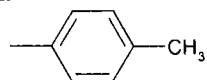
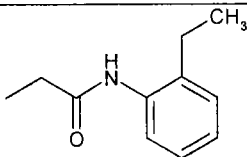
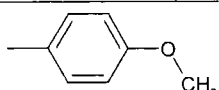
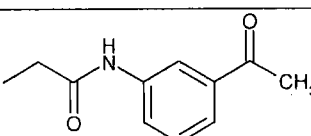
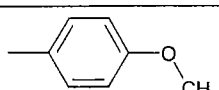
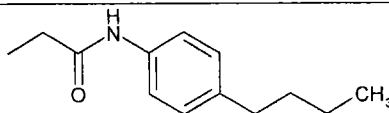
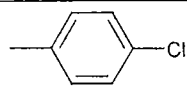
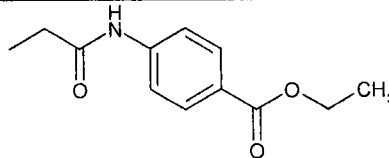
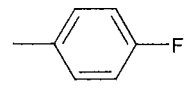
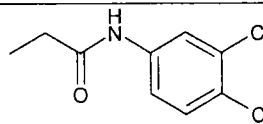
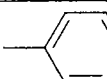
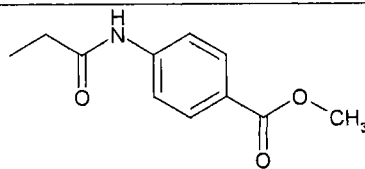
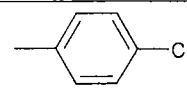
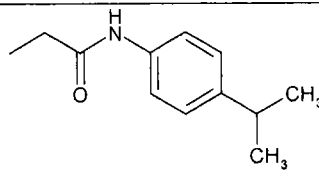
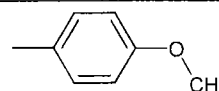
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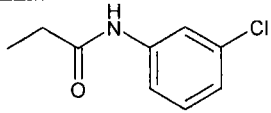
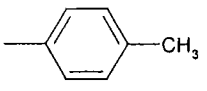
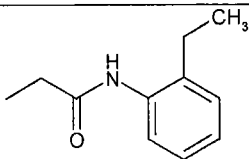
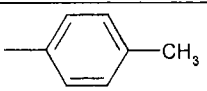
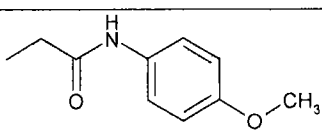
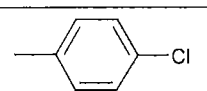
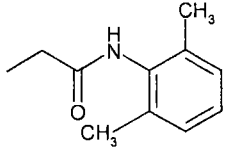
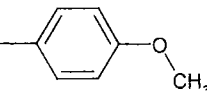
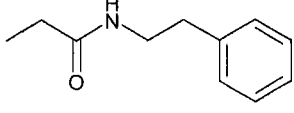
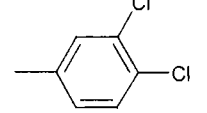
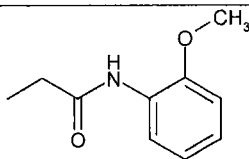
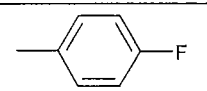
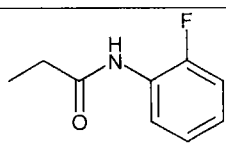
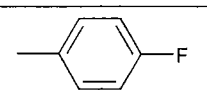
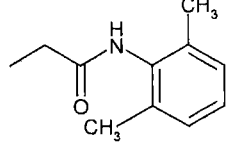
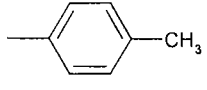
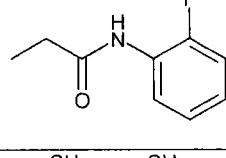
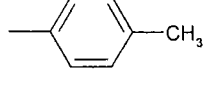
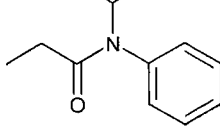
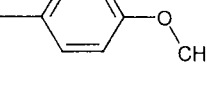
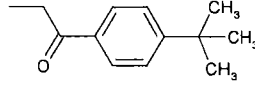
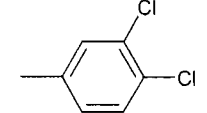
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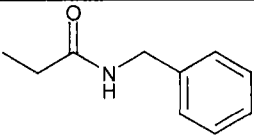
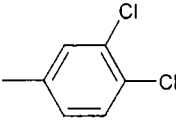
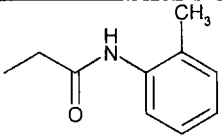
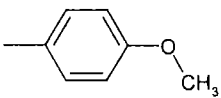
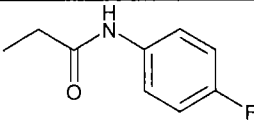
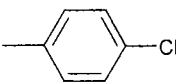
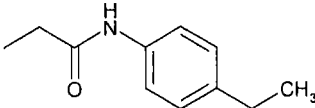
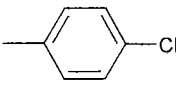
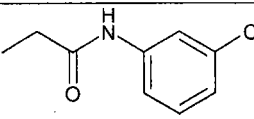
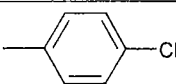
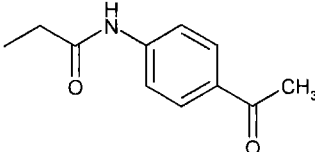
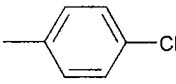
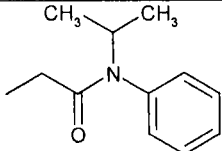
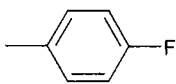
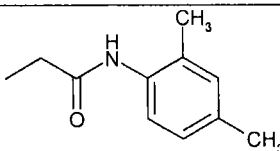
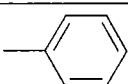
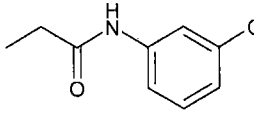
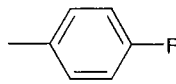
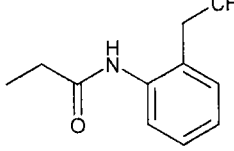
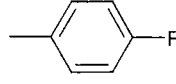
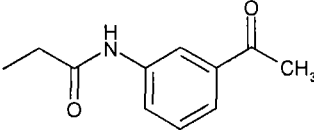
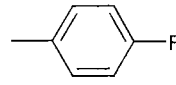
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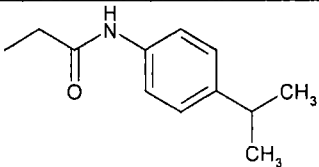
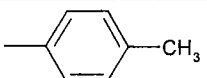
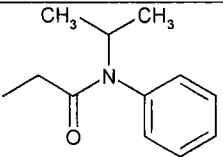
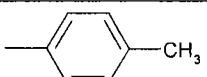
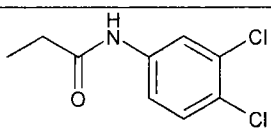
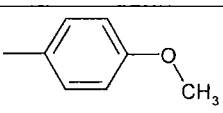
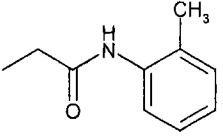
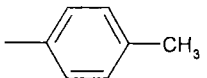
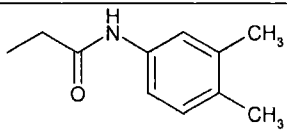
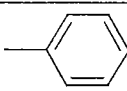
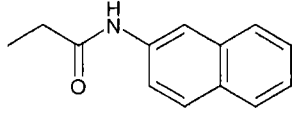
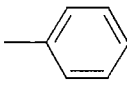
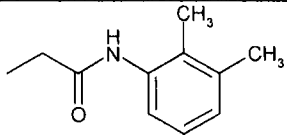
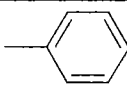
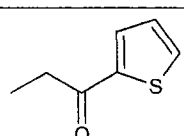
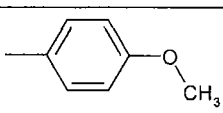
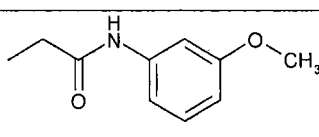
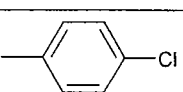
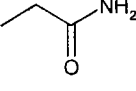
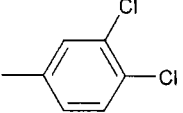
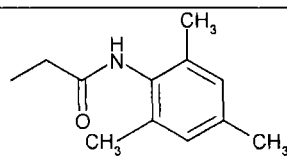
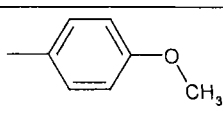
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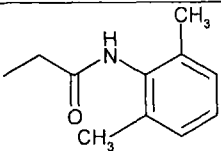
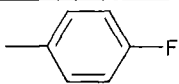
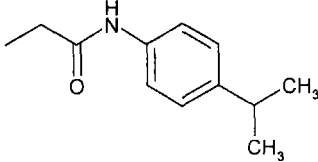
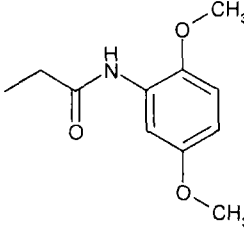
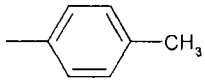
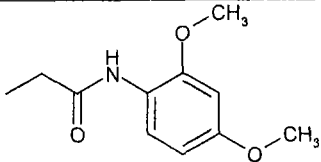
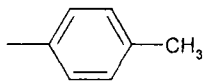
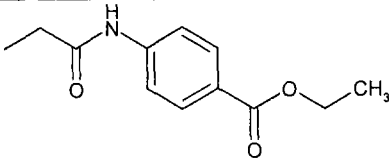
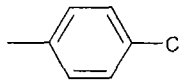
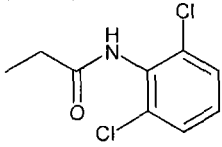
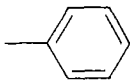
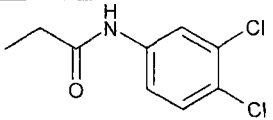
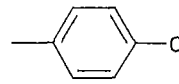
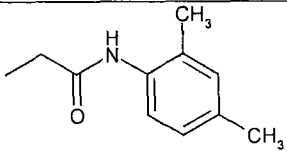
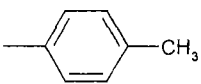
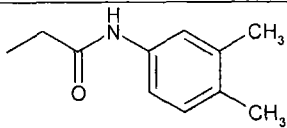
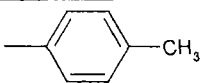
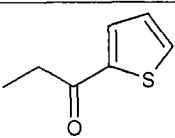
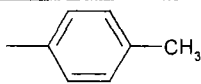
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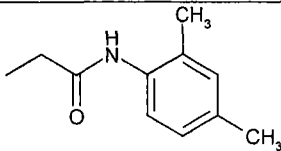
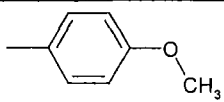
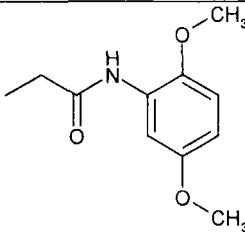
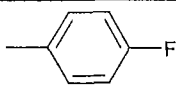
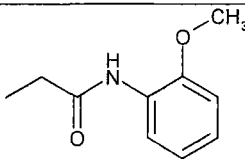
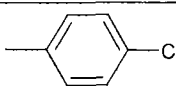
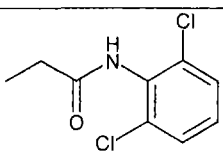
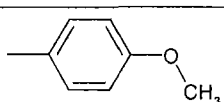
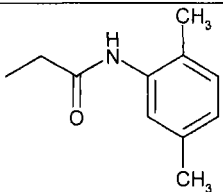
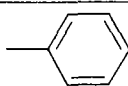
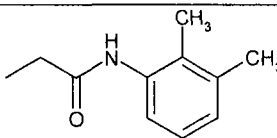
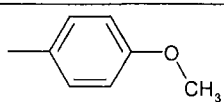
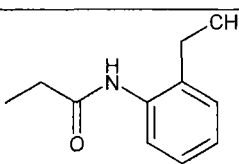
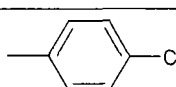
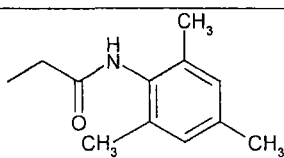
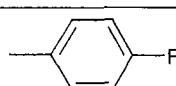
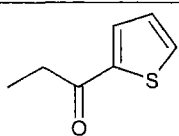
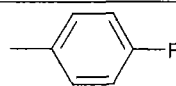
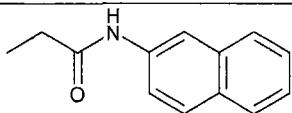
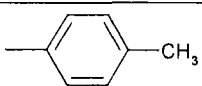
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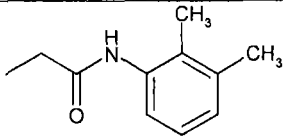
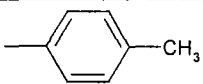
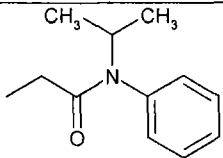
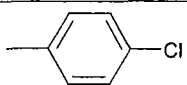
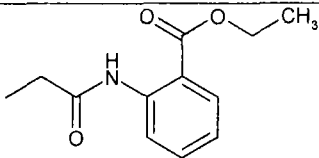
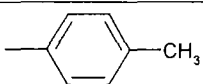
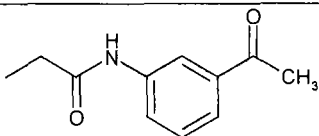
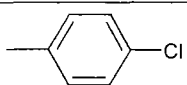
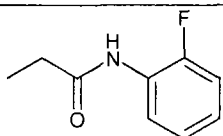
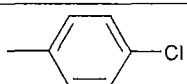
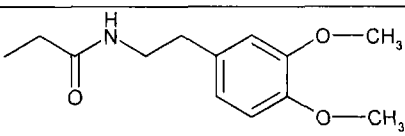
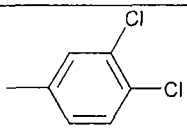
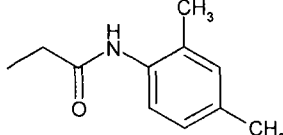
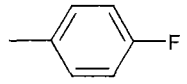
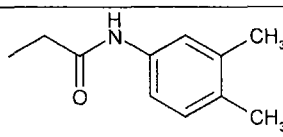
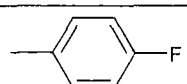
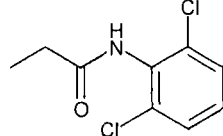
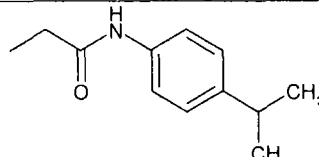
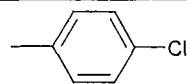
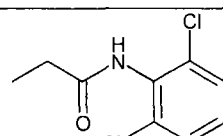
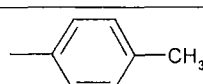
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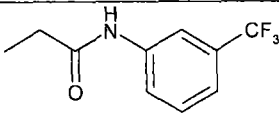
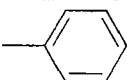
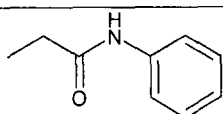
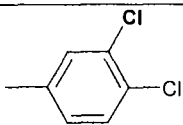
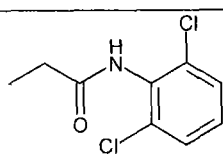
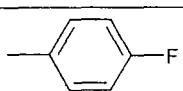
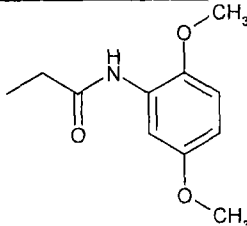
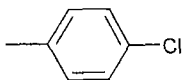
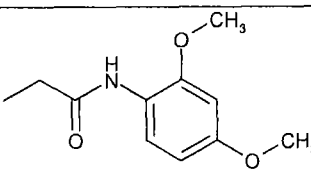
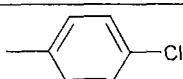
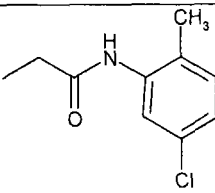
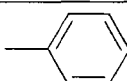
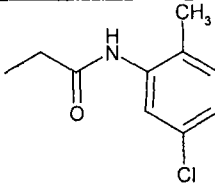
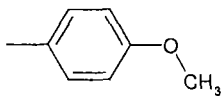
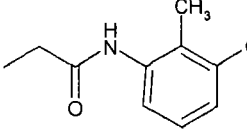
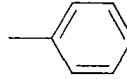
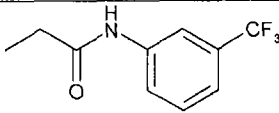
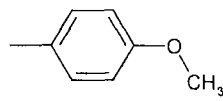
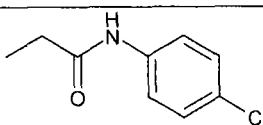
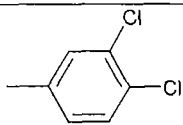
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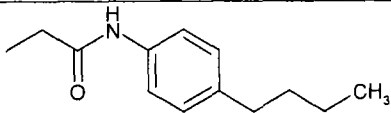
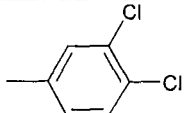
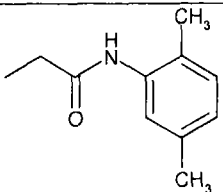
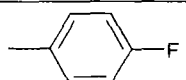
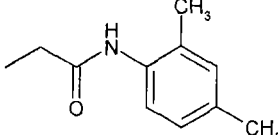
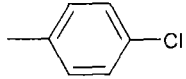
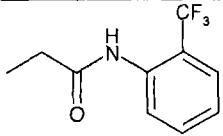
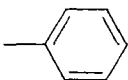
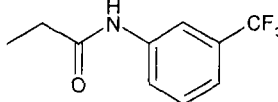
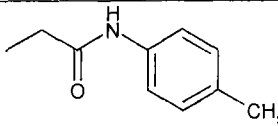
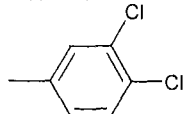
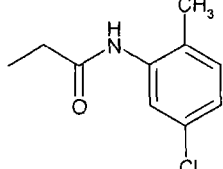
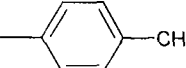
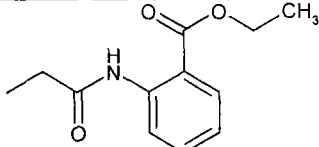
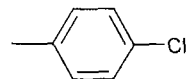
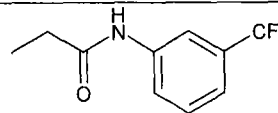
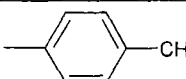
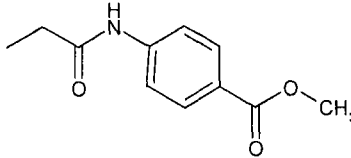
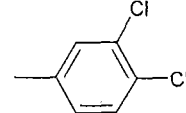
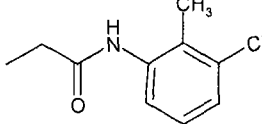
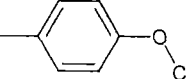
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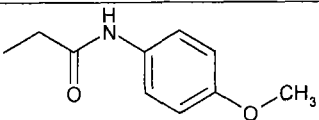
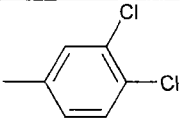
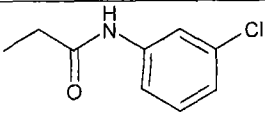
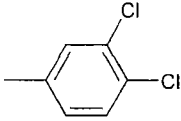
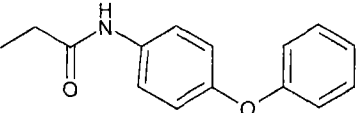
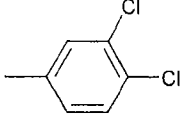
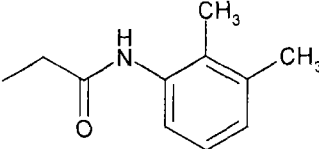
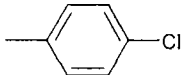
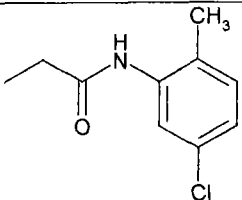
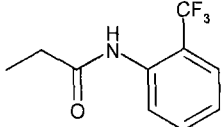
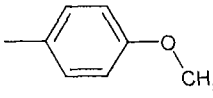
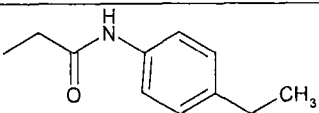
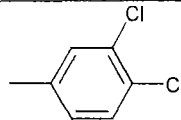
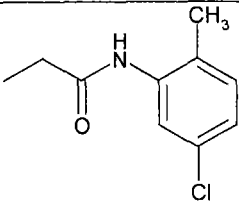
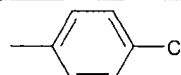
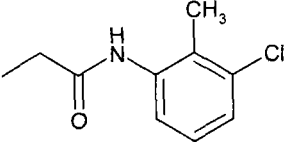
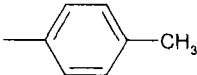
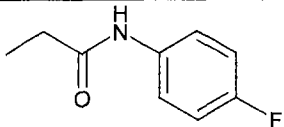
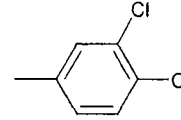
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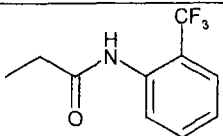
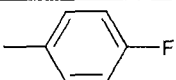
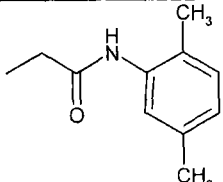
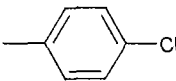
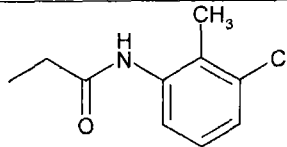
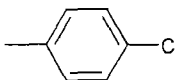
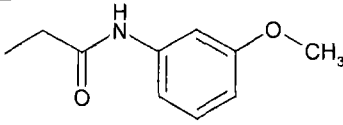
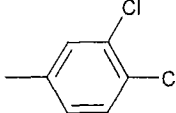
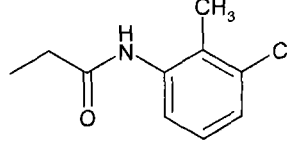
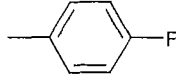
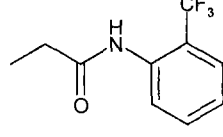
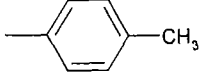
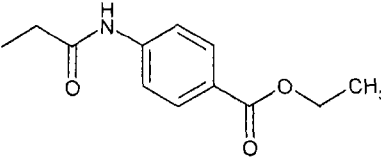
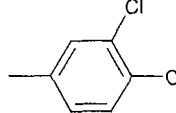
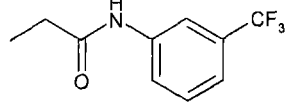
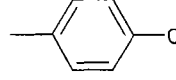
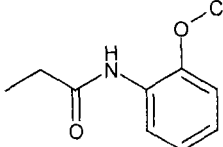
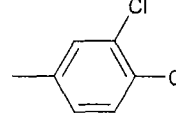
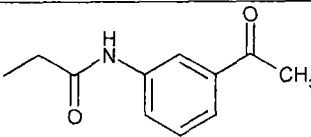
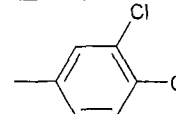
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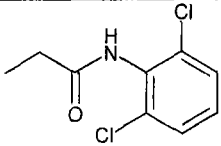
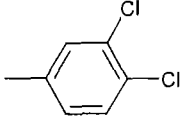
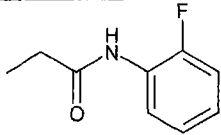
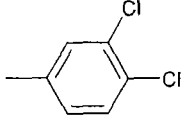
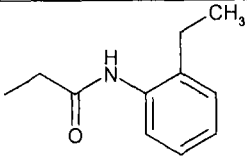
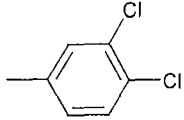
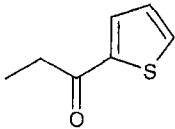
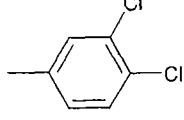
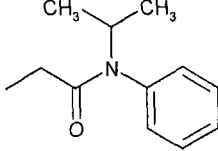
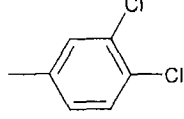
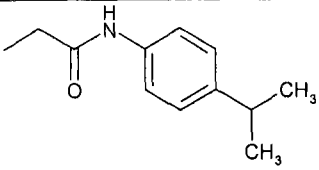
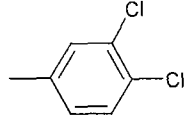
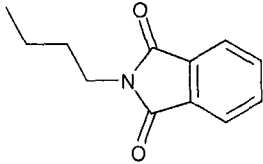
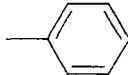
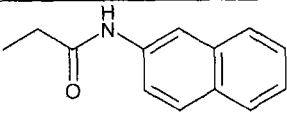
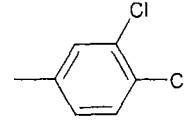
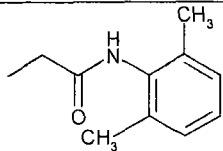
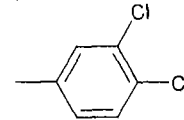
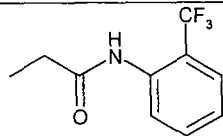
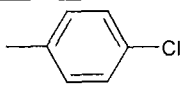
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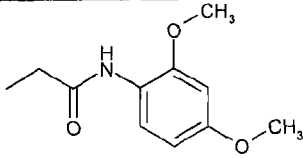
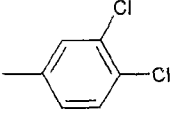
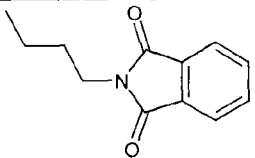
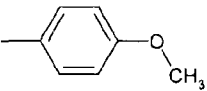
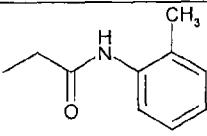
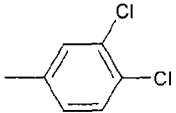
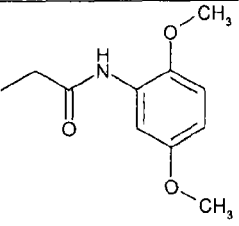
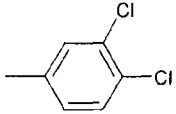
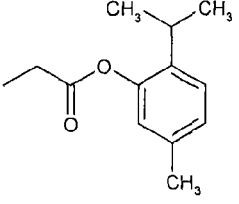
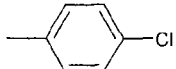
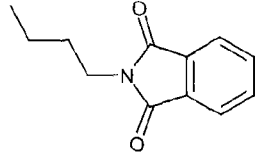
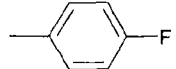
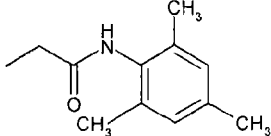
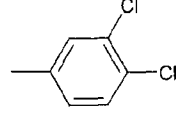
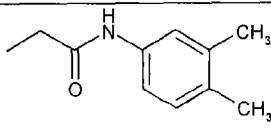
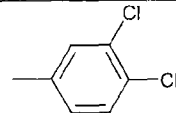
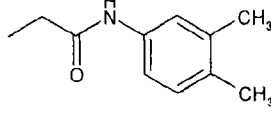
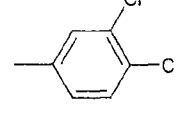
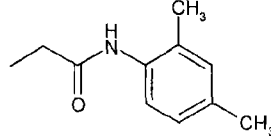
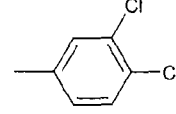
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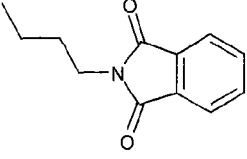
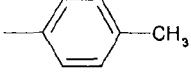
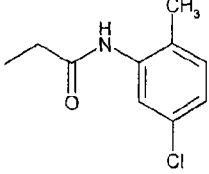
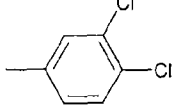
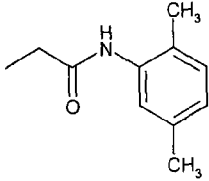
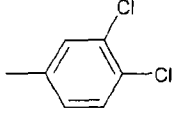
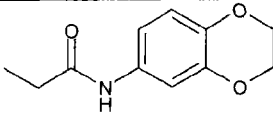
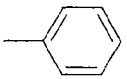
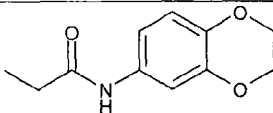
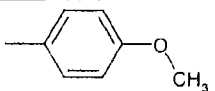
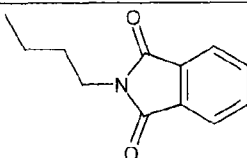
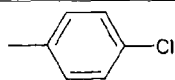
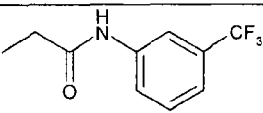
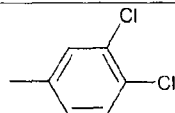
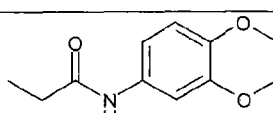
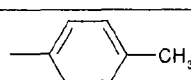
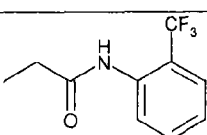
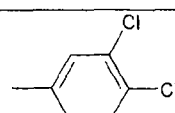
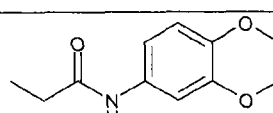
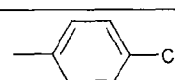
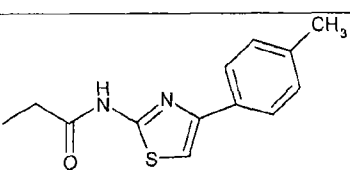
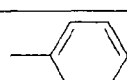
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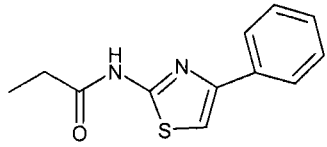
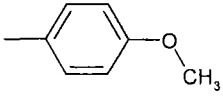
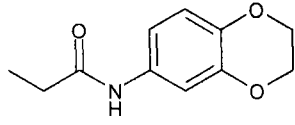
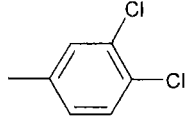
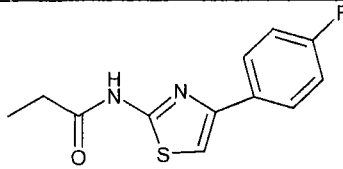
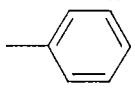
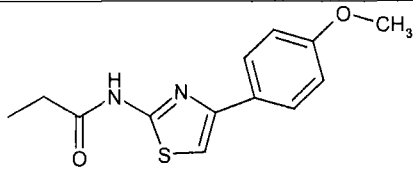
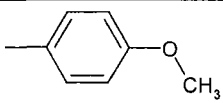
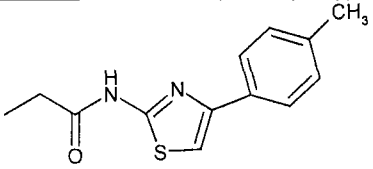
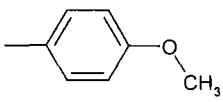
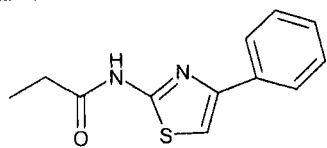
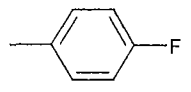
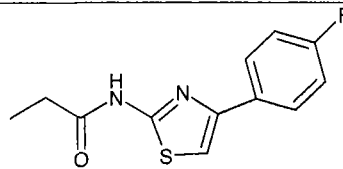
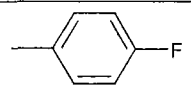
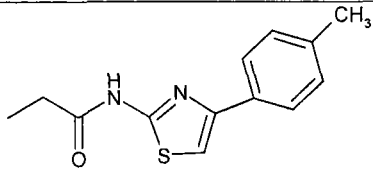
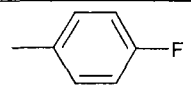
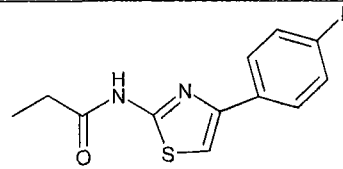
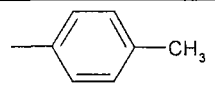
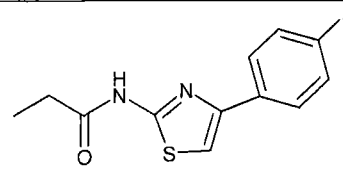
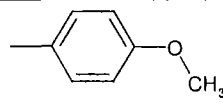
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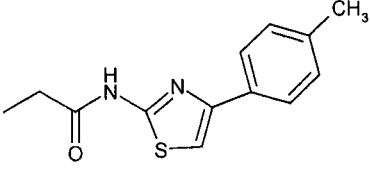
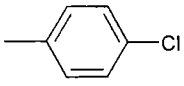
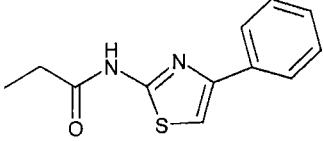
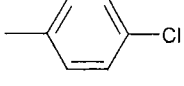
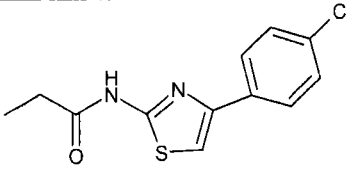
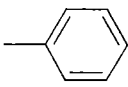
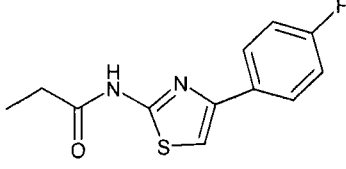
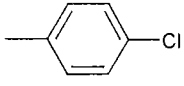
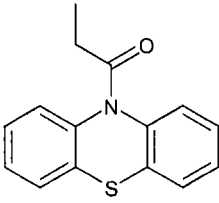
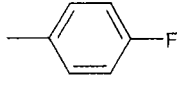
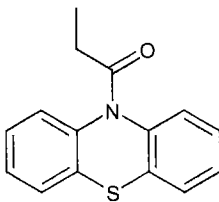
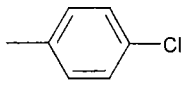
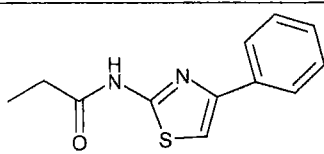
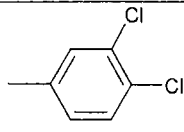
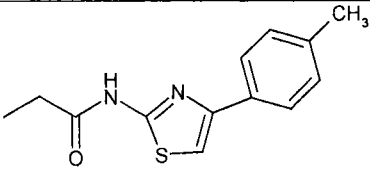
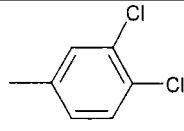
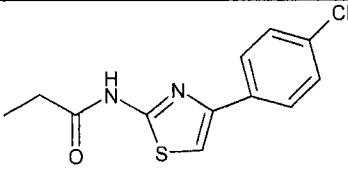
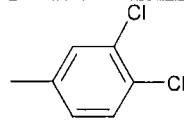
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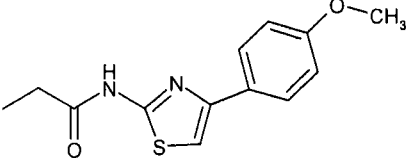
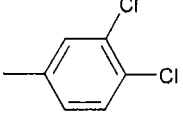
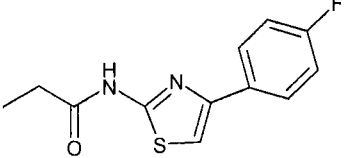
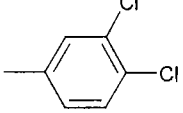
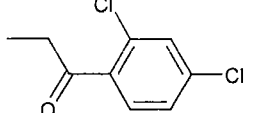
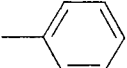
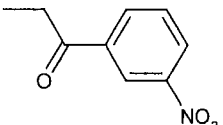
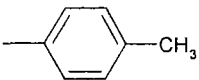
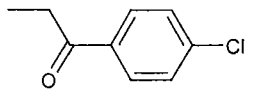
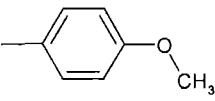
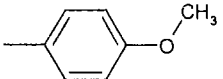
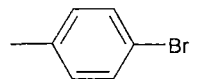
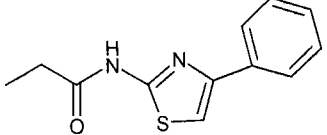
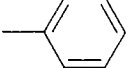
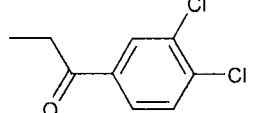
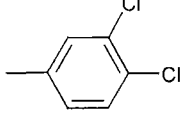
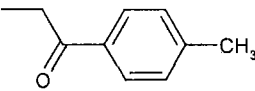
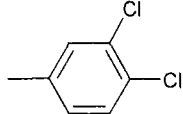
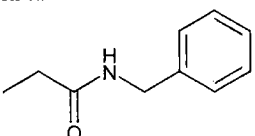
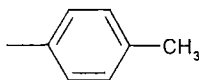
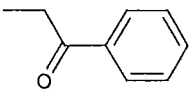
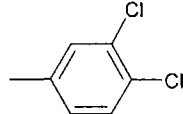
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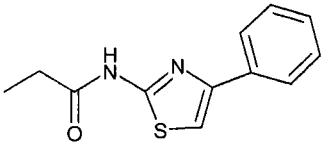
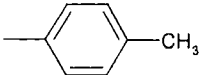
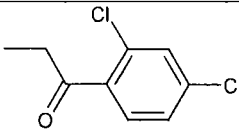
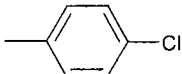
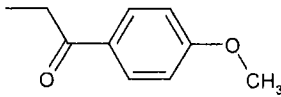
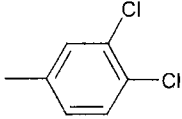
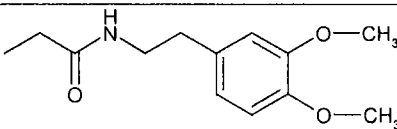
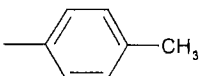
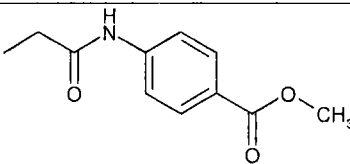
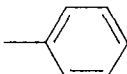
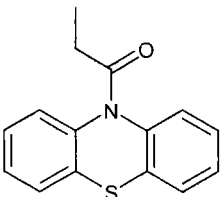
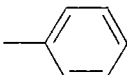
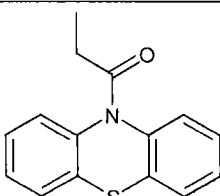
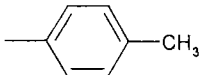
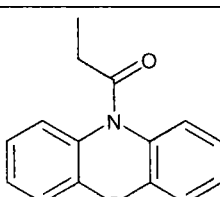
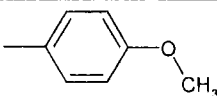
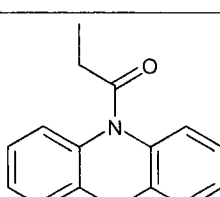
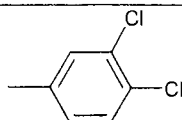
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¹H-NMR 谱(DMSO-d₆, 400 MHz):

实施例 239:

9.88 (s, 1H), 7.98 (s, 1H), 7.68 (d, J=3 Hz, 1H), 7.55 (d, J=8 Hz, 2H), 7.35 (d, J=8 Hz, 2H), 7.00 (d, J=9 Hz, 1H), 6.67 (dd, J=8, 3 Hz, 1H), 5.22 (s, 2H), 4.50 (m, 2H), 3.81 (s, 3H), 3.56 (s, 3H), 3.20 (m, 2H), 2.73 (m, 2H), 2.36 (s, 3H)。

实施例 241:

10.54 (s, 1H), 8.16 (s, 1H), 7.98 (d, J=2.1 Hz, 1H), 7.83 (d, J=8.4 Hz, 1H), 7.67 (dd, J=8.4, 2.1 Hz, 1H), 7.51 (d, J=10 Hz, 2H), 6.91 (d, J=10 Hz, 2H), 5.13 (s, 2H), 4.55 (m, 2H), 3.71 (s, 3H), 3.23 (m, 2H), 2.73 (m, 2H)。

实施例 322:

9.90 (s, 1H), 8.16 (s, 1H), 7.98 (d, J=2.1 Hz, 1H), 7.83 (d, J=8.4 Hz, 1H), 7.66 – 7.71 (m, 2H), 7.00 (d, J=9.0 Hz, 1H), 6.67 (dd, J=9.0, 3.1 Hz, 1H), 5.24 (s, 2H), 4.55 (m, 2H), 3.82 (s, 3H), 3.65 (s, 3H), 3.22 (m, 2H), 2.73 (m, 2H)。

实施例 341:

10.56 (s, 1H), 8.15 (s, 1H), 7.97 (d, J=2.1 Hz, 1H), 7.82 (d, J=8.4 Hz, 1H), 7.67 (dd, J=8.4, 2.1 Hz, 1H), 7.22 (d, J=2.5 Hz, 1H), 6.98 (dd, J=8.7, 2.5 Hz, 1H), 6.81 (d, J=8.7 Hz, 1H), 5.12 (s, 2H), 4.55 (m, 2H), 4.20 (m, 4H), 3.24 (m, 2H), 2.74 (m, 2H)。

实施例 373:

8.52 (t, J=5.5 Hz, 1H), 7.88 (2, 1H), 7.54 (d, J=8.1 Hz, 2H), 7.35 (d, J=8.1 Hz, 2H), 6.85 (d, J=8.1 Hz, 1H), 6.81 (d, J=1.9 Hz, 1H), 6.72 (dd, J=8.1, 1.9 Hz, 1H), 4.87 (s, 2H), 4.48 (m, 2H), 3.73 (s, 3H), 3.69 (m, 3H), 3.34 (m, 2H), 3.09 (m, 2H), 2.65 – 2.73 (m, 4H), 2.35 (s, 3H)。