巴豆烷型二萜及该类化合物抗HIV活性的构效关系和作用机制研究进展

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摘要: 巴豆烷型二萜为巴豆的主要活性成分, 是生物活性多样的大环二萜类化合物。其抗人类免疫缺陷病毒(human immunodeficiency virus, HIV) 活性在艾滋病治疗中具有独特优势和巨大潜力, 有望开发成为抗艾滋病临床试验的候选药物。本文回顾了近年来有关巴豆中巴豆烷型二萜成分及该类化合物抗HIV活性的研究进展, 进行系统的比较, 归纳了目前在巴豆中所发现巴豆烷型二萜类化合物, 总结了该类化合物的化学结构和生物活性关系, 同时简要讨论了巴豆烷型二萜抗HIV活性的作用机制的研究动态, 以期为进一步开发利用该类化合物提供参考, 同时也为巴豆的运用提供新的思路。

关键词: 巴豆烷型二萜; 巴豆; 抗HIV活性; 构效关系; 作用机制

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Research progress on structure activity relationship and mechanism of tigliane-type diterpenoids and their anti HIV activities

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Abstract: Tigliane-type diterpenoids are the main active components of croton and a diverse group of macrocyclic diterpenes with diverse biological activities. Their anti-HIV activity have unique advantages and great potential in the treatment of acquired immunodeficiency syndrome (AIDS), and were expected to be developed as a candidate drug for clinical trials of anti-AIDS. This article reviews the research progress on the components of tigliane-type diterpenoids in croton and their anti-HIV activity in recent years, conducts systematic comparisons, summarizes the currently discovered tigliane-type diterpenoids in croton. Their chemical structures and biological activity relationship were summarized. The research progress on the mechanism of tigliane-type diterpenoids' anti-HIV activity was briefly discussed. This research could provide guidance for further development and utilization of coumarin type diterpenes, as well as new ideas for the application of croton.

Key words: tigliane-type diterpenoid; croton; anti-HIV activity; structure-activity relationship; mechanism

巴豆烷型二萜 (tigliane-type diterpenoids) 是一类重要的大环二萜类化合物, 主要存在于大戟科和瑞香科植物中。近年来, 部分巴豆烷型二萜及其衍生物因其显著的药理活性而备受关注, 它们中的多数具有良好的抗病毒活性。然而, 这类化合物在具有高效生物活性的同时, 其促炎与促癌活性等不良反应限制了其进一步的开发利用。由于生物活性与其结构紧密相关, 在母体结构上的微小变化都会使其生物活性改变[1], 因此, 系统归纳其构效关系和作用机制显得尤为重要。

针对人类免疫缺陷病毒 (human immunodeficiency virus, HIV) 引起的艾滋病, 目前的高效抗逆转录病毒治疗 (highly active antiretroviral therapy, HAART) 虽然

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可以有效抑制HIV, 但不能完全根除病毒感染。因此, 抗HIV研究越来越侧重于消除潜伏病毒库的策略。目前, 部分巴豆烷型二萜表现出了良好的抗HIV活性。例如, 12-脱氧佛波醇-13-乙酸酯 (prostratin) 是一种有效的抗HIV药物[2], 其与部分巴豆烷型二萜在结构和活性上的差异为研究巴豆烷型二萜的构效关系提供了思路。

本文回顾了近年来有关巴豆中巴豆烷型二萜成分及该类化合物抗HIV活性的研究进展, 进行系统的比较, 总结了目前在巴豆中所发现的106种巴豆烷型二萜类化合物, 并简要讨论了巴豆烷型二萜在抗HIV活性方面的构效关系及作用机制的研究动态。

1 巴豆中的巴豆烷型二萜

对于巴豆的化学成分研究, 国内外学者更多地将重点放在巴豆种子的研究上, 巴豆油是巴豆种子中的主要成分, 同时也是药效活性成分, 但也是一种毒性成分, 可刺激皮肤, 并具有广泛的生物活性, 包括抗HIV、促进肿瘤、细胞毒性和促炎等特性。其主要化学成分是巴豆烷型二萜类化合物。

巴豆烷型二萜由5/7/6/3四环系统组成, 包括五元环A、七元环B、六元环C和环丙烷系统D, 它们依次稠合组成了这类二萜类化合物。通常情况下, 该类化合物的A环C-3位置含有一个α,β-不饱和酮基团。

目前, 从巴豆中分离得到的巴豆烷型二萜多数为佛波醇二萜酯类, 基于佛波醇, 巴豆烷型二萜类衍生物可以根据结构中的官能团差异分为: 佛波酯型、C-4脱氧佛波酯型、C-17取代佛波酯型、C-12脱氧佛波酯型及其他类型 (图1)。在此之前, 从大戟科和瑞香科植物中共发现300余种巴豆烷型二萜类化合物[3]。

佛波醇 (phorbol) 最初是从大戟科植物巴豆 (*Croton tiglium*) 中分离得到的, 在1967年由Hecker等[4]确定了其结构 (图1)。其分子结构中包含的5个羟基易于发生官能团反应, 形成各种酯类衍生物。巴豆中所分离出的二萜类成分主要是佛波醇二萜酯类, 本部分综述了目前巴豆中所发现的巴豆烷型二萜类化合物, 表1[5-35]列出了巴豆中的巴豆烷型二萜 (**1**～**106**) 及部分半合成产物 (**107**～**130**), 图2展示了巴豆烷型二萜的化学结构。

1.1 佛波酯型巴豆烷二萜

巴豆中已知的佛波酯型巴豆烷二萜见表1和图2 (**1**～**85**), 其主要来源于巴豆的种子及其油脂, 而在巴豆枝叶发现的较少。佛波醇 (**15**) 是佛波醇酯的母体二萜, A环位于左侧, 与B环相连。这些化合物中, 6元C环以顺式方式与环丙烷D环相连。它们含有对酰化具有不同反应活性的羟基, 佛波醇中的醇羟基表现出的反应顺序为C20-OH > C13-OH > C12-OH > C4-OH > C9-OH[34]。关于佛波醇的结构改性研究一直在进行, 主要针对C20、C13和C12羟基进行结构修饰。

在巴豆中, 大多数佛波酯以12,13-或13,20-二酯的形式存在, 而少数佛波酯则以12,13,20-三酯或单酯的形式存在。从巴豆的种子和枝叶中分离出来的几种特殊的佛波酯 (**81**～**84**)[13,14], 通过广泛的核磁共振波谱和质谱分析阐明了其结构。在C-6位, 这些特殊的佛波酯带有醛官能团, 代替了羟甲基。其中, 化合物**84**是首个具有20-醛基的天然佛波酯。而从巴豆种子中分离得到的crotonianoid C (**85**)[21]是首个具有10*R*-构型的佛波酯。

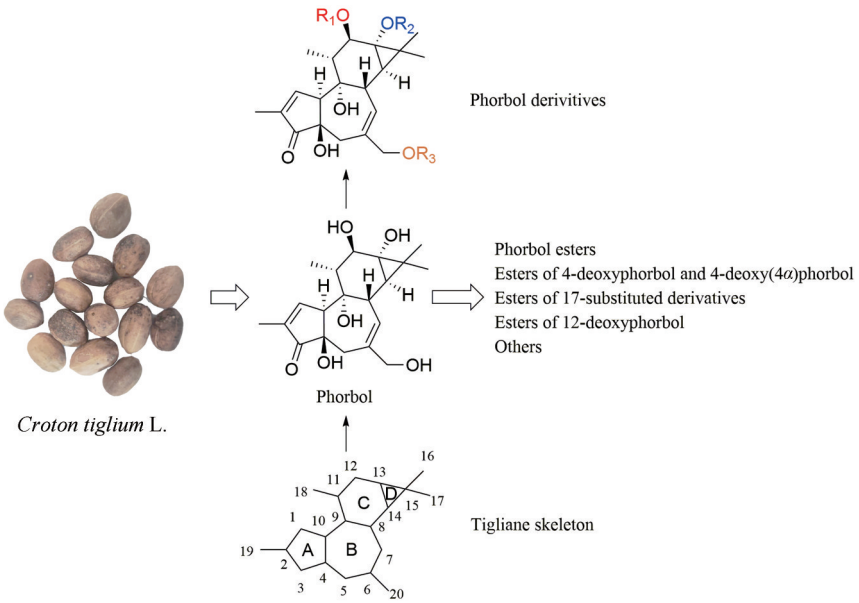


Figure 1 Framework and classification of tigliane-type diterpenoids

Table 1 Tigliane-type diterpenoids (**1**−**106**) and some semi synthetic products (**107**−**130**) in croton

No.	Compound name	Part of plant	Ref.
Phorbol ester			
1	12-*O*-(2-Methyl)butyrylphorbol-13-tiglate	The seeds	[5]
2	12-*O*-Tiglylphorbol-13-propionate	The seeds	[5]
3	13-*O*-Acetylphorbol-20-oleate	The seeds	[5]
4	12-*O*-Tiglylphorbol-13-decanoate	Croton oil	[6]
5	12-*O*-Tetradecanoylphorbol-13-acetate	Croton oil	[6]
6	12-*O*-Benzoylphorbol-13-benzoate	Croton oil	[7]
7	13-*O*-Acetylphorbol-20-linoleate	The seeds	[8]
8	13-*O*-Tigloylphorbol-20-linoleate	The seeds	[8]
9	12-*O*-Acetylphorbol-13-tigliate	The seeds	[8]
10	12-*O*-Decanoylphorbol-13-(2-methyl)butyrate	The seeds	[8]
11	12-*O*-Tigloylphorbol-13-(2-methyl)butyrate	The seeds	[8]
12	12-*O*-(2-Methyl)butyroylphorbol-13-dodecanoate	The seeds	[8]
13	12-*O*-(2-Methyl)butyrylphorbol-13-octanoate	The branches and leaves	[9]
14	12-*O*-Isobutyrylphorbol-13-decanoate	The branches and leaves	[9]
15	Phorbol	The seeds	[10]
16	12-*O*-Decanoylphorbol-13-acetate	The seeds	[6]
17	12-*O*-Dodecanoylphorbol-13-acetate	The seeds	[6]
18	12-*O*-Hexadecanoylphorbol-13-acetate	The seeds	[6]
19	12-*O*-Tiglylphorbol-13-butyrate	The seeds	[6]
20	12-*O*-Methylbutyrylphorbol-13-dodecanoate	The seeds	[6]
21	12-*O*-Methylbutyrylphorbol-13-decanoate	The seeds	[6]
22	12-*O*-Acetylphorbol-13-dodecanoate	The seeds	[6]
23	12-*O*-Octanoylphorbol-13-methylbutyrate	The seeds	[6]
24	12-*O*-Tiglylphorbol-13-octanoate	The seeds	[6]
25	12-*O*-Acetylphorbol-13-decanoate	The seeds	[6]
26	12-*O*-Tiglylphorbol-13-dodecanoate	The seeds	[6]
27	12-*O*-Butyrylphorbol-13-dodecanoate	The seeds	[6]
28	12-*O*-Tiglylphorbol-13-isobutyrate	Croton oil	[11]
29	12-*O*-(2-Methyl)butyrylphorbol-13-isobutyrate	Croton oil	[11]
30	Phorbol-12-tigliate	Croton oil	[11]
31	12-*O*-Acetylphorbol-13-acetate	Croton oil	[11]
32	12-*O*-Tiglylphorbol-13-acetate	Croton oil	[11]
33	Phorbol-13-acetate	Croton oil	[11]
34	13-*O*-(2-Methyl)butyrylphorbol	The leaves	[12]
35	Phorbol-13-dodecanoate	The seeds	[13]
36	Phorbol-12-isobutyrate	The seeds	[13]
37	12-*O*-(2-Methyl)butyrylphorbol-13-aetate	The seeds	[13]
38	12-*O*-Tiglylphorbol-13-isobutyrate	The seeds	[13]
39	Phorbol-12-(2-methy)butyrate	The seeds	[13]
40	Phorbol-12-tetradecanoate	The seeds	[13]
41	Phorbol-13-aetate	The seeds	[13]
42	Phorbol-13-decanoate	The seeds	[13]
43	12-*O*-(2-Methyl)butyrylphorbol-13-dodecanoate	The seeds	[8]
44	12-*O*-Acetylphorbol-13-isobutyrate	The branches and leaves	[14]
45	12-*O*-Benzoylphorbol-13-(2-methyl)butyrate	The branches and leaves	[14]
46	12-*O*-Dodecanoyl-13-*O*-acetylphorbol-20-linolenate	The seeds	[15]
47	20-Acetylphorbol-13-*O*-(2-methyl)butyrate	The leaves	[16]
48	12-*O*-Acetylphorbol-13-(2-methyl)butyrate	The leaves	[16]
49	(2′*S*)12-*O*-2-(Methyl)butyryl-phorbol-13-(4*Z*)-decanoate	The leaves	[17]
50	(2′*S*)12-*O*-2-(Methyl)butyryl-phorbol-13-(4*Z*,7*Z*)-decanoate	The leaves	[17]
51	12-*O*-Tigloyl-phorbol-13-(4*Z*)-decanoate	The leaves	[17]
52	12-O-Tigloyl-phorbol-13-(4*Z*,7*Z*)-decanoate	The leaves	[17]
53	20-Acetyl-13-*O*-(2-methyl)butyryl-phorbol	The seeds	[18]
54	12-*O*-(2-Methyl)butyrylphorbol-13-phenylacetate	The seeds	[19]
55	12-*O*-Tiglylphorbol-13-phenylacetate	The seeds	[19]
56	12-*O*-Acetyl-5,6-didehydro-7-oxophorbol-13-yl 2-methylbutanoate	The leaves	[15]
57	12-*O*-Acetyl-5,6-didehydro-7-oxophorbol-13-yl 2-methylpropanoate	The leaves	[15]

Continued

No.	Compound name	Part of plant	Ref.
58	Tiglin A	The leaves	[14]
59	7-Oxo-5-ene-phorbol-13-(2-methyl)butyrate	The leaves	[12]
60	7-Keto-12-*O*-tiglylphorbol-13-acetate	The seeds	[13]
61	7-Keto-phorbol-12-tiglate	The seeds	[13]
62	7-Keto-phorbol-12-(2-methyl)butyrate	The seeds	[13]
63	7-Keto-phorbol-13-acetate	The seeds	[13]
64	12-*O*-Tiglyl-7-oxo-5-ene-phorbol-13-(2-methyl)butyrate	The branches and leaves	[14]
65	13-*O*-Isobutyryl-7-oxo-6,7-dihydrophorbol-5-ene	The leaves	[17]
66	12-*O*-Tiglyl-13-*O*-phenylacetate-7-oxo-6,7-dihydrophorbol-5-ene	The seeds	[19]
67	Crotignoid A	The branches and leaves	[20]
68	Crotignoid B	The branches and leaves	[20]
69	Crotignoid C	The branches and leaves	[20]
70	Crotignoid D	The branches and leaves	[20]
71	Crotignoid E	The branches and leaves	[20]
72	Crotignoid F	The branches and leaves	[20]
73	Crotignoid G	The branches and leaves	[20]
74	Crotignoid H	The branches and leaves	[20]
75	Crotignoid I	The branches and leaves	[20]
76	Crotignoid J	The branches and leaves	[20]
77	12-*O*-Isobutyrylphorbol-13-acetate	The branches and leaves	[20]
78	12-*O*-Acetyl-5,6-didehydro-6,7-dihydro-7-hydroxyphorbol-13-yl 2-methylbutanoate	The leaves	[15]
79	7-Hydroxyl-phorbol-5-ene-13-(2-methyl)butyrate	The leaves	[12]
80	7-Hydroxyl-phorbol-5-ene-13-isobutyrate	The leaves	[12]
81	20-Formylphorbol-12-tiglate	The seeds	[13]
82	20-Formylphorbol-13-dodecanoate	The seeds	[13]
83	20-Formylphorbol-13-decanoate	The seeds	[13]
84	20-Deoxy-20-oxophorbol-12-tiglate13-(2-methyl)butyrate	The branches and leaves	[14]
85	10*β*-Phorbol-13-aetate	The seeds	[21]
4-Deoxyphorbol and 4-deoxy(4*α*)phorbol			
86	Crotignoid K	The branches and leaves	[20]
87	13-*O*-Acetyl-4-deoxy-4*α*-phorbol-20-linoleate	The seeds	[5]
88	13-*O*-Acetyl-4-deoxy-4*α*-phorbol-20-oleate	The seeds	[5]
89	12-*O*-Tiglyl-4-deoxy-4*α*-phorbol-13-decanoate	The seeds	[5]
90	12-*O*-Tiglyl-4-deoxy-4*α*-phorbol-13-phenylacetate	The seeds	[5]
91	12-*O*-Tiglyl-4-deoxy-4*α*-phorbol-13-(2-methyl)butyrate	The seeds	[5]
92	12-*O*-Tiglyl-4-deoxy-4*α*-phorbol-13-isobutyrate	Croton oil	[11]
93	12-*O*-Tiglyl-4-deoxy-4*α*-phorbol-13-acetate	Croton oil	[11]
94	12-*O*-(2-Methyl)butyryl-4-deoxy-4*α*-phorbol-13-acetate	Croton oil	[11]
95	4-Deoxy-4*α*-phorbol-13-acetate	Croton oil	[11]
96	Tiglin B	The leaves	[14]
97	12-*O*-Tiglylphorbol-4-deoxy-4*β*-phorbol-13-acetate	The seeds	[22]
98	12-*O*-Tiglylphorbol-4*β*-deoxy-4-phorbol-13-hexadecanoate	The seeds	[22]
99	13-*O*-Acetylphorbol-4-deoxy-4*β*-phorbol-20-oleate	The seeds	[22]
100	13-*O*-Acetylphorbol-4-deoxy-4*β*-phorbol-20-linoleate	The seeds	[22]
101	4-Deoxy-20-oxophorbol12-tiglyl-13-acetate	The leaves	[12]
17-Substituted derivatives			
102	13-Acetyl-12,17-di-*O*-tiglylphorbol	The stems	[23]
Others			
103	Crotonianoid A	The seeds	[21]
104	Crotonianoid B	The seeds	[21]
105	Crotonols A	The leaves	[24]
106	Crotonols B	The leaves	[24]
107	Phorbol-12,13,20-trieicosapentaenoate	Semisynthesis	[25]
108	Phorbol-13-arachidonate	Semisynthesis	[25]
109	Phorbol-12,13-dicosapentaenoate	Semisynthesis	[25]
110	Phorbol-12,13-dihydroeicosanoate	Semisynthesis	[25]
111	Phorbol-12-arachidonate	Semisynthesis	[25]

Continued

No.	Compound name	Part of plant	Ref.
112	12-*O*-Tetradecanoyl phorbol-20-acetate	Semisynthesis	[25]
113	12,13-Didecyl phorbol	Semisynthesis	[26]
114	12,13-Di-6-bromohexylphorbol	Semisynthesis	[26]
115	Phorbol-12,13-cinnamate	Semisynthesis	[27]
116	Phorbol-12,13-dihydrocinnamate	Semisynthesis	[27]
117	12-*O*-Cinnamoylphorbol-13-butyrate	Semisynthesis	[27]
118	Phorbol-12-methylsuberate-13-acetate	Semisynthesis	[28]
119	12-*O*-20-*O*-Diacetylphorbol-13-decanoate	Semisynthesis	[29]
120	12-*O*-Tetradecanoylphorbol-13,20-diacetate	Semisynthesis	[29]
121	3*β*-Hydroxyphorbol-12,13,20-triacetate	Semisynthesis	[29]
122	Phorbol-12,13,20-triacetate	Semisynthesis	[29]
123	Phorbol-12,13-dihexanoate	Semisynthesis	[30]
124	4*α*-Phorbol-12,13-didecanoate	Semisynthesis	[30]
125	12-*O*-(Methoxymethyl)phorbol-13-decanoate	Semisynthesis	[31]
126	*Phorbol ester 1	Semisynthesis	[32]
127	*Phorbol ester 2	Semisynthesis	[32]
128	S11	Semisynthesis	[33]
129	12-(Trans-4-fluorocinnamoyl)-13-decanoylphorbol	Semisynthesis	[34]
130	Phorbol-13-stearate	Semisynthesis	[35]

*Phorbol ester 1 = 1-(4-((((1a*R*,1b*S*,4a*R*,7a*S*,7b*S*,8*R*,9*R*,9a*S*)-9a-acetoxy-4a,7b-dihydroxy-3-(hydroxymethyl)-1,1,6,8-tetramethyl-5-oxo-1a,1b,4,4a,5,7a,7b,8,9,9a-decahydro-1*H*-cyclopropa[3,4]benzo[1,2-e]azulen-9-yl)oxy)carbonyl)-3-(perfluorobutyl)phenyl)-1-oxo-2,5,8,11-tetraoxatridecan-13-oic acid

*Phorbol ester 2 = 1-(4-((((1a*R*,1b*S*,4a*R*,7a*S*,7b*S*,8*R*,9*R*,9a*S*)-9a-acetoxy-4a,7b-dihydroxy-3-(hydroxymethyl)-1,1,6,8-tetramethyl-5-oxo-1a,1b,4,4a,5,7a,7b,8,9,9a-decahydro-1*H*-cyclopropa[3,4]benzo[1,2-e]azulen-9-yl)oxy)carbonyl)-3-(perfluorohexyl)phenyl)-1-oxo-2,5,8,11-tetraoxatridecan-13-oic acid

1.2 C-4脱氧佛波酯型巴豆烷二萜

C-4脱氧佛波酯型巴豆烷二萜的碳骨架与佛波醇的碳骨架相似, 不同之处在于C-4处的*β*-OH基团被*β*-H或*α*-H所取代。4-脱氧-4*α*-佛波醇和4-脱氧-4*β*-佛波醇虽然在化学结构上非常相似, 但核磁共振氢谱仍然是一种有效的区分手段。具体来说, 对于4-脱氧-4*α*-佛波醇和4-脱氧-4*β*-佛波醇骨架, H-1、H-4和H-5的化学位移表现出显著的差异[22]。从巴豆叶中分离得到具有20-醛基的4-脱氧-4*α*-佛波醇酯 (**101**), 这种化合物显示出有效的抗结核活性[12]。目前, 巴豆中发现的C-4脱氧佛波酯型巴豆烷二萜大多源自巴豆种子及其油脂, 巴豆中已知的C-4脱氧佛波酯型巴豆烷二萜见表1和图2 (**86**～**101**)。

1.3 C-17取代佛波酯型巴豆烷二萜

C-16或C-17取代的佛波酯型巴豆烷二萜与其他类型的化合物区别在于环丙烷上C-16或C-17处具有额外的伯羟基或酯基。目前, 仅在 *Croton tiglium* L. var. *xiaopadou* 的茎中分离得到一种C-17取代佛波酯型巴豆烷二萜 (**102**)。

1.4 其他类型的巴豆烷二萜

除了上述基于佛波醇官能团差异而分类的巴豆烷型二萜类衍生物, 近年来一些学者还发现了一些碳链骨架各异的巴豆烷二萜类化合物。例如, crotonianoid A和B (**103**, **104**) 是从巴豆种子中分离得到的, 其相对构型是通过核Overhauser效应光谱实验确定的, 并通过X-ray单晶衍射分析进一步证实。crotonianoid A具有独特的13,14-和13,15-diseco-tigliane骨架, 而crotonianoid B包含一个不同寻常的五元$C_{(13)}$−O−O−$C_{(15)}$过氧环。

研究指出, 巴豆烷型二萜中环丙烷环的裂解可能会赋予该类化合物一定的抗肿瘤活性[21]。另外, 从巴豆叶中分离得到的crotonols A和B (**105**, **106**) 是两种含有罕见C-7/C-14环化和5/7/7三环碳骨架的巴豆烷型二萜类化合物[24]。巴豆中已知的其他类型巴豆烷二萜可在表1和图2 (**103**～**106**) 中找到。

2 巴豆烷型二萜类化合物抗HIV活性的构效关系研究

这类化合物具有丰富的生物活性, 包括抗HIV、激活人间充质干细胞、抗结核特性、抗肿瘤、诱导血小板聚集、促癌、促炎、抗白血病、杀虫和抗肝纤维化活性等[12,13,18,36-44]。目前, 针对巴豆烷型二萜的研究主要聚焦在其抗肿瘤与抗HIV活性上, 由于该类化合物具有促炎和促癌的活性, 致使它们作为抗HIV药物的潜在应用受到了限制。

佛波醇酯类化合物结构上的差异明显影响其生物活性。然而, 天然产物分离难, 含量低等问题, 成为研究佛波醇酯类化合物生物活性及其构效关系时必须克服的障碍。半合成目标化合物为研究佛波醇酯类化合

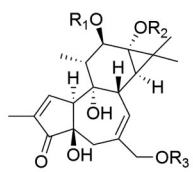
物构效关系提供了途径。同时, 巴豆油的水解能为巴豆烷型二萜的合成提供较低成本和较短生产周期的原料, 通过选择性羟基保护、酯化和脱保护等方法对佛波醇进行结构修饰, 可以得到佛波醇酯化衍生物。佛波醇酯衍生物的合成途径如图3所示。对于C-12脱氧佛波酯型巴豆烷二萜, 由于prostratin表现出优秀的抗HIV活性, 且不具有促肿瘤活性, 因此其与部分促肿瘤的巴豆烷型二萜在结构上的差异引起了广泛关注。

2.1 C-12脱氧佛波酯型巴豆烷二萜

从巴豆油中分离出的化合物**5** (图2) 能够完全抑制HIV-1诱导的细胞病变作用 (IC_{100} = 0.48 μg·L^{-1})[29], 但其以促炎活性而著称, 在药理学和生物化学研究中常被用于诱导炎症反应。而prostratin在感染HIV-l的人淋巴细胞中具有强大的细胞保护作用。在结构上, 它与已知的促肿瘤佛波酯相似, 能够抑制新发HIV-1感染, 同时上调潜伏前病毒的病毒表达, 显示出与其他佛波醇酯相似的抗HIV活性模式。然而, prostratin本身似乎不具有促肿瘤活性[38], 因此具有作为HAART的诱导辅助疗法的潜力。

Wang等[45]总结了当时所发现的12-脱氧佛波酯型巴豆烷二萜生物活性, 并推测该类化合物的抗HIV-1和促肿瘤活性与C-13处酰基的类型有关。短链酰基通常有利于抗HIV-1活性, 而长链酰基有效增强了促肿瘤活性。目前prostratin天然来源较少, 且含量低, 因其与佛波醇在结构上的微小差异, Wender等[46]以佛波醇为原料, 经过五步反应, 成功合成了prostratin, 为

A



21 R_1=methyl butyryl, R_2=decanoyl, R_3=H
22 R_1=acetyl, R_2=dodecanoyl, R_3=H
23 R_1=octanoyl, R_2=methyl butyryl, R_3=H
24 R_1=tiglyl, R_2=octanoyl, R_3=H
25 R_1=acetyl, R_2=decanoyl, R_3=H

35 R_1=H, R_2=dodecanoyl, R_3=H
36 R_1=isobutyryl, R_2=R_3=H
37 R_1=(2-methyl)butyryl, R_2=acetyl, R_3=H
38 R_1=tiglyl, R_2=isobutyryl, R_3=H
39 R_1=(2-methyl)butyryl, R_2=R_3=H

48 R_1=acetyl, R_2=(2-methyl)butyryl, R_3=H
49 R_1=(2-methyl)butyryl, R_2=(4*Z*)decenoyl, R_3=H
50 R_1=(2-methyl)butyryl, R_2=(4*Z*,7*Z*)decenoyl, R_3=H
51 R_1=tiglyl, R_2=(4*Z*)decenoyl, R_3=H
52 R_1=tiglyl, R_2=(4*Z*,7*Z*)decenoyl, R_3=H

1 R_1=(2-methyl)butyryl, R_2=tiglyl, R_3=H
2 R_1=tiglyl, R_2=propionyl, R_3=H
3 R_1=H, R_2=acetyl, R_3=oleoyl
4 R_1=tiglyl, R_2=decanoyl, R_3=H
5 R_1=tetradecanoyl, R_2=acetyl, R_3=H

11 R_1=tiglyl, R_2=(2-methyl)butyryl, R_3=H
12 R_1=(2-methyl)butyryl, R_2=dodecanoyl, R_3=H
13 R_1=(2-methyl)butyryl, R_2=octanoyl, R_3=H
14 R_1=isobutyryl, R_2=decanoyl, R_3=H
15 R_1=R_2=R_3=H

26 R_1=tiglyl, R_2=dodecanoyl, R_3=H
27 R_1=butyryl, R_2=dodecanoyl, R_3=H
28 R_1=tiglyl, R_2=isobutyryl, R_3=H
29 R_1=(2-methyl)butyryl, R_2=isobutyryll, R_3=H
30 R_1=tiglyl, R_2=R_3=H

40 R_1=tetradecanoyl, R_2=R_3=H
41 R_1=H, R_2=acetyl, R_3=H
42 R_1=H, R_2=decanoyl, R_3=H
43 R_1=(2-methyl)butyryl, R_2=dodecanoyl, R_3=H

6 R_1=benzoyl, R_2=benzoyl, R_3=H
7 R_1=H, R_2=acetyl, R_3=$C_{18}H_{31}O$
8 R_1=H, R_2=tiglyl, R_3=$C_{18}H_{31}O$
9 R_1=acetyl, R_2=tiglyl, R_3=H
10 R_1=decanoyl, R_2=(2-methyl)butyryl, R_3=H

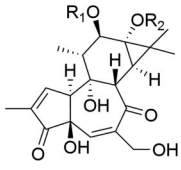
16 R_1=decanoyl, R_2=acetyl, R_3=H
17 R_1=dodecanoyl, R_2=acetyl, R_3=H
18 R_1=hexadecanoyl, R_2=acetyl, R_3=H
19 R_1=tiglyl, R_2=butyryl, R_3=H
20 R_1=methyl butyryl, R_2=dodecanoyl, R_3=H

31 R_1=R_2=acetyl, R_3=H
32 R_1=tiglyl, R_2=acetyl, R_3=H
33 R_1=H, R_2=acetyl, R_3=H
34 R_1=H, R_2=(2-methyl)butyryl, R_3=H

44 R_1=acetyl, R_2=isobutyryl, R_3=H
45 R_1=benzoyl, R_2=(2-methyl)butyryl, R_3=H

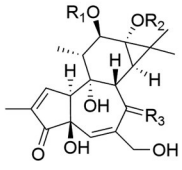
46 R_1=dodecanoyl, R_2=acetyl, R_3=linoleoyl
47 R_1=H, R_2=(2-methyl)butyryl, R_3=acetyl

53 R_1=H, R_2=(2-methyl)butyryl, R_3=acetyl
54 R_1=(2-methyl)butyryl, R_2=phenylacetyl, R_3=H
55 R_1=tiglyl, R_2=phenylacetyl, R_3=H

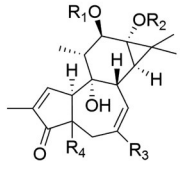


56 R_1=acetyl, R_2=(2-methyl)butyryl
57 R_1=acetyl, R_2=isobutyryl
58 R_1=acetyl, R_2=(2-methyl)propionyl
59 R_1=H, R_2=(2-methyl)butyryl
60 R_1=tiglyl, R_2=acetyl
61 R_1=tiglyl, R2=H

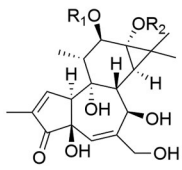
62 R_1=(2-methyl)butyryl, R_2=H
63 R_1=H, R_2=acetyl
64 R_1=tiglyl, R_2=(2-methyl)butyryl
65 R_1=H, R_2=isobutyryl
66 R_1=tiglyl, R_2=phenylacetyl



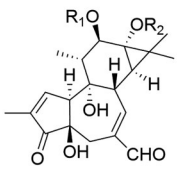
67 R_1=tiglyl, R_2=(2-methyl)butyryl, R_3=H,ß-OOH
68 R_1=tiglyl, R_2=isobutyryl, R_3=H,ß-OOH
69 R_1=tiglyl, R_2=(2-methyl)butyryl, R_3=H,ß-OH
70 R_1=tiglyl, R_2=isobutyryl, R_3=H,ß-OH
71 R_1=tiglyl, R_2=isobutyryl, R_3=O
72 R_1=tiglyl, R_2=propionyl, R_3=O
73 R_1=H, R_2=decanoyl, R_3=O



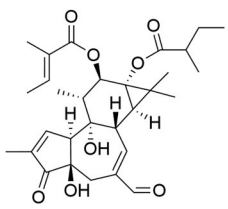
74 R_1=tiglyl, R_2=isobutyryl, R_3=CHO, R_4=ß-OH
75 R_1=(2-methyl)butyryl, R_2=(2-methyl) butyryl, R_3=CH_2OH, R_4=ß-OH
76 R_1=benzoyl, R_2=isobutyryl, R_3=CH_2OH, R_4=ß-OH
77 R_1=isobutyryl, R_2=acetyl, R_3=CH_2OH, R_4=ß-OH



78 R_1=acetyl, R_2=(2-methyl)butyryl
79 R_1=H, R_2=(2-methyl)butyryl
80 R_1=H, R_2=isobutyryl



81 R_1=tiglyl, R_2=H
82 R_1=H, R_2=dodecanoyl
83 R_1=H, R_2=decanoyl



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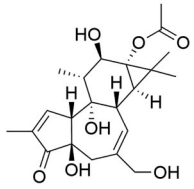

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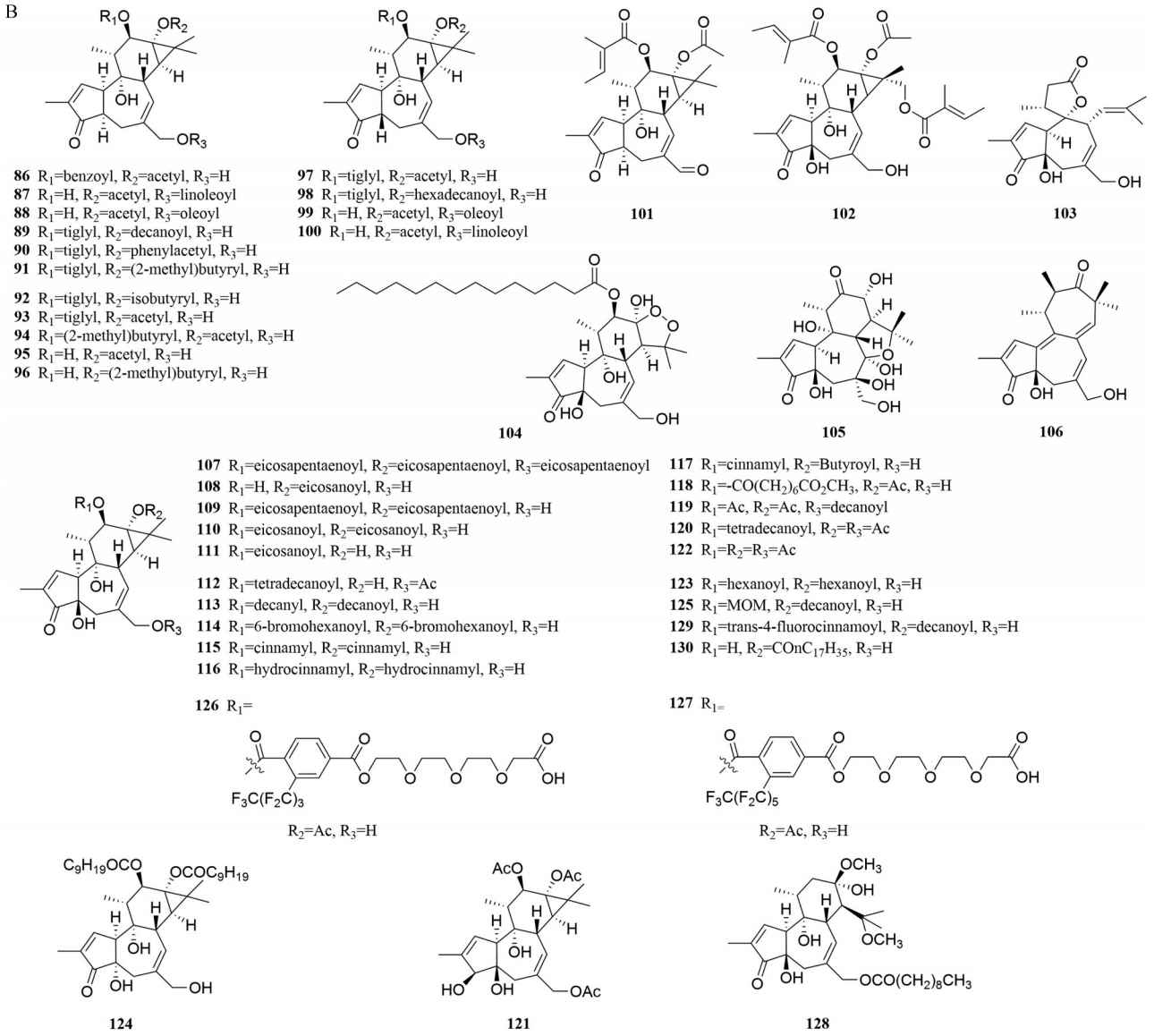

Figure 2 Chemical structures of tigliane-type diterpenoids. A: **1**−**85**; B: **86**−**130**

prostratin的合成提供了一条简单的途径。

2.2 佛波酯型巴豆烷二萜

2.2.1 C-12和C-13位结构修饰 Márquez等[35]合成了一系列佛波醇-13-单酯, 使用了人急性T淋巴细胞白血病细胞作为HIV-1潜伏期的细胞模型, 研究它们拮抗HIV-1潜伏期的能力。研究表明, 含有中等或长脂肪族脂肪酸链的佛波醇-13-单酯是HIV-1潜伏期的有效拮抗剂, 佛波醇-13-乙酸酯 (EC_{50} > 5 μmol·L^{-1}) 与prostratin (EC_{50} = 0.41 μmol·L^{-1}) 相比, 因存在12-羟基而完全无活性, 但可以通过增加酰基部分的长度来诱导活性。化合物**125** (EC_{50} = 0.03 μmol·L^{-1}) 的效力至少是prostratin的10倍, 其活性随着酰基侧链的缩短而迅速下降。

在Li等[47]的研究中, 合成并在人T细胞白血病(human acute lymphoblastic leukemia cells, MT-4) 细胞中通过HIV-1的实验室病毒株NL4-3复制筛选测定评估了新的佛波酯衍生物, 发现抗HIV活性通常与C-13位的酰基酯有关。化合物**5**的位置异构体与佛波醇-13-乙酸酯类均未显示出活性, 两种活性的大量损失由化合物**5**中的长酰基被去除所致。而在12-*O*-乙酰基-13-*O*-酰基佛波醇衍生物中, 化合物**25** (IC_{100} = 7.6 μg·L^{-1}) 的脂肪酸碳链数量的增加和减少都导致了HIV-1诱导的细胞病变效应 (cytopathic effect, CPE) 抑制的显著降低[29], 表明该类化合物抗HIV活性对其取代基具有碳数依赖性。

在酯侧链上具有苯环的佛波醇-12,13-二酯表现出优异的抗HIV活性, 其中化合物**115**具有良好的安全性指数 (safety index, SI > 500)[47]。过去的研究表明,

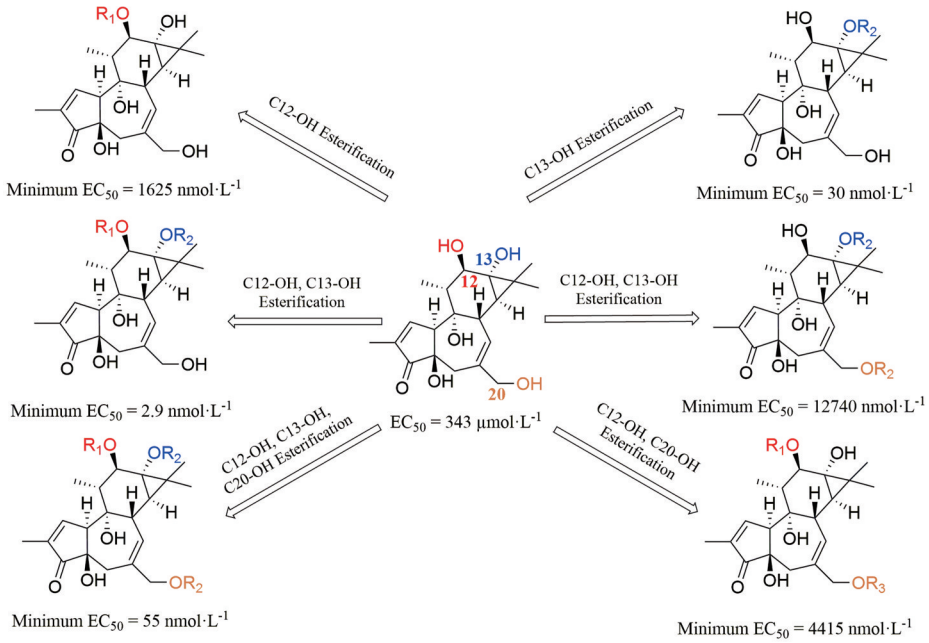

Figure 3 Synthetic routes of phorbol ester derivatives and the strongest anti HIV activity of various derivatives in current research

12-*O*-肉桂酰佛波醇-13-乙酯中肉桂酸的苯环上引入吸电子基团时活性增加, 反之引入给电子基时活性下降[27]。在此基础上, 利用优势基团理论和药效团拼合理论, 创新地设计和合成了一系列佛波酯, 观察对HIV-1诱导的人T淋巴细胞白血病细胞的细胞病变效应的抑制作用。13-癸酰基-佛波醇-12-反式肉桂酰衍生物表现出了其优越性, 尤其是那些在肉桂酰结构中具有对位吸电子基团的衍生物, 如化合物**129**表现出最有效的抗HIV-1活性 (EC_{50} = 2.9 nmol·L^{-1}), 还显示出作为蛋白激酶C (protein kinase C, PKC) 激活剂的潜力。与具有-OCH_3或-OCH_2O-等供电子基团的衍生物相比, 在12-反式肉桂酰佛波醇衍生物中引入对位吸电子基团(如氟、氯或溴) 显著增强了其抗HIV-1活性, 有明显的趋势表明, 取代基的吸电子能力越强 (-F > -Cl > -Br), 抗HIV-1活性就越大[34]。

对于C-12和C-13位具有相同取代基的化合物, 长链脂肪酸酯中化合物**113**活性最好EC_{50}值为4.6 nmol·L^{-1}; 含溴脂肪酸酯中化合物**114**活性最好EC_{50}值为5.7 nmol·L^{-1}。它们的活性都随着取代基碳链的增长或缩短而大大减小, 同样具有碳数依赖性[26]。化合物**115** (IC_{50} = 9.21 nmol·L^{-1}) 被还原成化合物**116** (IC_{50} = 0.49 nmol·L^{-1}) 后, 其抗HIV活性提升[27], 提示取代基的不饱和度减小可能有利于其抗HIV活性。

2.2.2 C-12, C-13和C-20位及其他结构修饰 佛波醇-12,13,20-三酯的活性通常明显低于单酯和二酯, 这可能是因为C-20处的羟基酯化[27]。在之后的研究中, Huang[26]合成了一系列不同的单酯, 双酯和三酯化合物, 对HIV-1在人T淋巴细胞白血病细胞中复制的抑制活性进行评价研究, 结果显示C-20处的羟基酯化会导致抗HIV活性降低甚至消失。值得注意的是, C-13和C-20处由相同酸酯化但C-12处由不同酸修饰的佛波醇三酯表现出高效的抗HIV活性[34]。

化合物**5**中20-OH和4-OH的乙酰化显著降低了对CPE的抑制作用。此外, 在化合物**121** (IC_{100} = 500 μg·mL^{-1}) 与**122** (IC_{100} = 62.5 μg·mL^{-1}) 中观察到C-3羰基的还原降低了对CPE的抑制作用[29]。

2.2.3 四环结构修饰 El-Mekkawy等[29]制备了佛波醇和异佛波醇的48种衍生物, 以HIV-1诱导的MT-4细胞CPE的抑制作用和它们对PKC的激活能力, 分别作为抗HIV-1和肿瘤促进活性的指标, 研究了它们的构效关系, 这两种活性通常在具有A/B反式构型的佛波醇衍生物中观察到, 但在具有A/B顺式构型的异佛波醇衍生物中则未观察到。后续研究表明, 具有反式稠合A/B构型的佛波醇衍生物具有较高的活性[34]。

Huang等[33]又评价了佛波醇的5种酸水解产物及它们各自的20-单酯对HIV-1诱导的合胞体形成的抑制作用, 结果表明, 环丙烷D的化学修饰可能会影响抗HIV-1活性和PKC结合亲和力。其中, 开环佛波醇衍生物S11 (**128**) 的EC_{50}为0.27 μmol·L^{-1}, 对HIV-1逆转录的中间产物具有有效的抑制作用, 对环丙烷D的化学修饰为该类化合物的研究拓宽了思路。

3 抗HIV作用机制研究进展

PKC属于磷脂依赖性丝氨酸/苏氨酸激酶家族[48], PKC亚型 (PKC isoforms, PKCs) 参与多种信号转导途

径。根据结构元件和辅因子需求，哺乳动物PKC分为四大类，包括经典PKCs、新型PKCs、非典型PKCs和PKC相关激酶。不同PKC的活性与环境相关，这些激酶可以是信号通路的正调节因子或负因子[49]。PKC作为已知的佛波醇酯类受体[42]，大部分生物学效果被认为是通过涉及该酶的信号通路诱导的。目前，研究表明巴豆烷型二萜的抗HIV活性机制中，蛋白激酶C亚型的激活十分重要。

3.1 激活病毒转录并下调受体表达

12-*O*-十四烷酰佛波醇-13-乙酸酯 (12-*O*-tetradecanoylphorbol-13-acetate, TPA) 是PKC的有效激活剂，其对HIV-1长末端重复序列的刺激作用主要依赖于通过核转录因子-κB (nuclear factor kappa-B, NF-κB) 通路的PKC活性[50,51]。进一步研究表明，prostratin激活经典的NF-κB通路，新型PKC在此过程中起着非常突出的作用[52]。在之后对prostratin如何诱导潜伏性HIV-1前病毒转录激活的分子机制的研究中，提出了通过PKCε/蛋白激酶D3 (protein kinase D3, PKD3)/NF-κB信号通路的机制，细胞外prostratin首先激活PKCε，导致PKD3激活环的磷酸化。磷酸化的PKD3具有活性并促进NF-κB的核易位，从而以κB元件依赖性方式导致HIV-1的转录激活[53] (图4)。

此外，12-*O*-巴豆酰基-13-*O*-异丁酰基-20-羟基-4β-脱氧佛波醇 (4β-dPE A)[54]是一种4-脱氧佛波醇酯衍生物，在HIV复制周期中，可通过激活NF-κB和PKCθ/丝裂原激活蛋白激酶激酶 (mitogen-activated protein kinase kinase, MEK) 在静息外周血单个核细胞中重新激活HIV。这与López-Huertas等[55]的发现相似，TPA激活PKCθ通过Ras蛋白/Raf蛋白激酶/MEK/细胞外信号调节激酶 (extracellular regulated protein kinases, ERK) 信号转导通路和下游含ETS域转录因子Elk1的激活，增强病毒转录 (图4)。

研究发现，prostratin通过激活经典和新型PKC亚型，诱导表面抗原分化簇4受体 (cluster of differentiation 4 receptors, CD4) 和CXC趋化因子受体4 (CXC chemokine receptor 4, CXCR4) 内化和降解，从而抑制新发HIV感染 (图4)。在相似剂量下，TPA在介导CD4和CXCR4下调方面比prostratin更有效[56]。

3.2 刺激A3G表达

Chen等[57]在大戟科植物 *Ostodes katharinae* 中分离得到新型佛波醇酯12-*O*-二十三烷酰基佛波醇-20-乙酸酯 (hop-8) 可抑制野生型HIV-1和人类免疫缺陷病毒2型毒株以及耐药株在人T淋巴细胞白血病细胞和静息外周血单个核细胞中的复制，并且具有较低的细胞毒性。与其他化合物相比，hop-8的主要机制之一是通过PKC通路刺激HIV-1感染的细胞中表达载脂蛋白B mRNA编辑酶催化多肽样蛋白3G (apolipoprotein B mRNA editing enzyme-catalytic polypeptide-like 3G,

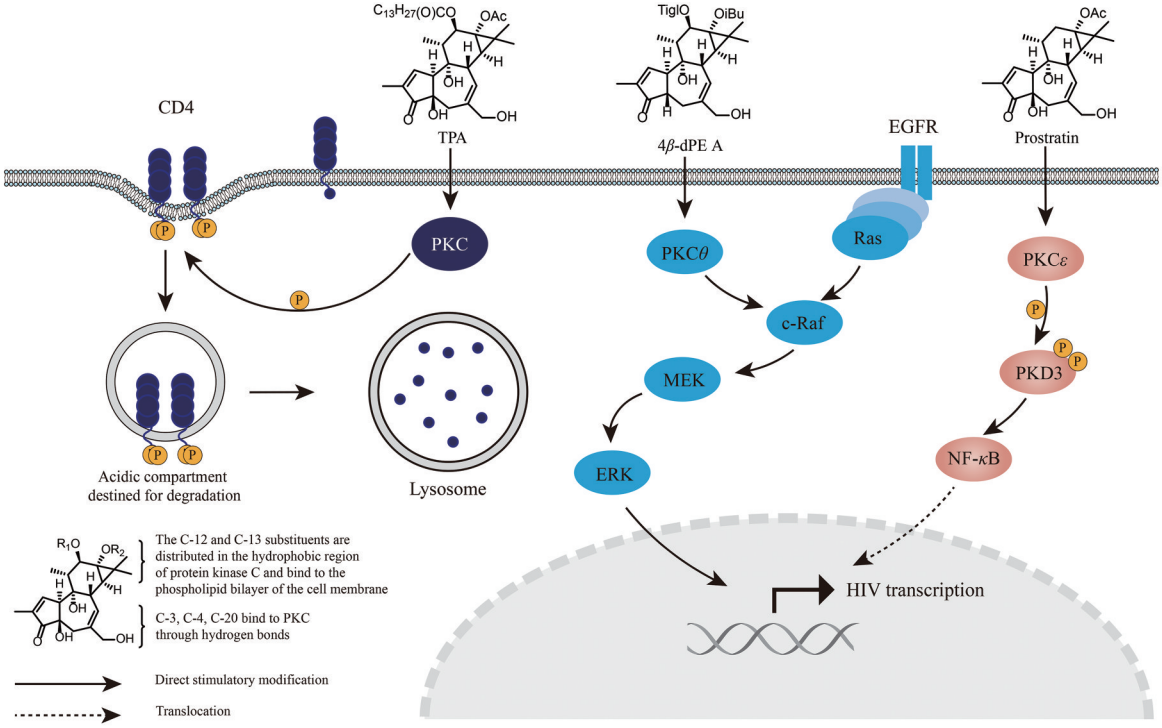

Figure 4 Schematic diagram of the mechanism of activating viral transcription and downregulating receptor expression. EGFR: Epidermal growth factor receptor

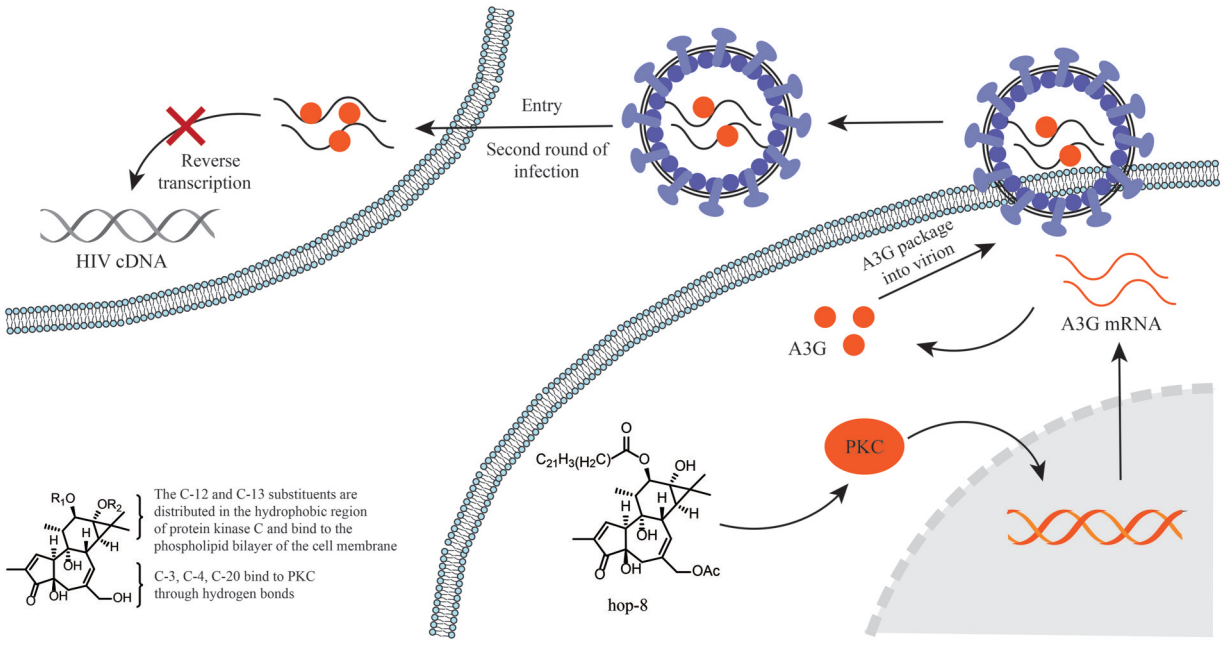

Figure 5 Schematic diagram of the anti HIV activity mechanism stimulated by A3G expression

A3G), 上调后代病毒粒子中的A3G水平, 限制后代病毒粒子的复制, 从而降低后代病毒的传染性 (图5)。这种抑制HIV复制的新机制可能代表了开发HIV感染新疗法的一种有前途的方法。

4 总结与展望

过去的研究指出, 佛波醇酯的抗HIV活性与取代基的碳数密切相关。而在母核结构中, 反式稠合的A/B环系统对这些化合物的抗HIV活性至关重要。近年来, 对构效关系的研究已从佛波醇与长链饱和脂肪酸的酯化反应转向以优势基团理论和药效团拼合理论, 设计合成佛波醇酯衍生物, 同时探索了C-13和C-14位环丙烷环D对抗HIV活性的影响。此外, 具有相似母核的化合物也会因取代基的不同而表现出不同的激活活性。在对此类化合物抗HIV作用机制的研究中, 不仅完善了先前的理论, 还不断有新的作用机制被提出。

综上所述, 巴豆作为一种传统中药, 其所富含的巴豆烷型二萜类化合物展现出了独特的价值与潜力。然而, 毒性和不良反应的问题是亟待解决的核心问题, 这为开发抗HIV药物带来了挑战。为了克服这些限制, 当前学者结合现代技术对其母核结构进行结构修饰, 旨在获取疗效更佳的化合物。此外, 优化给药策略等方法也可能是降低毒性的有效途径。

另外, 生物利用度和稳定性也是制约其临床应用的关键因素。巴豆烷型二萜类化合物在体内的吸收、分布、代谢和排泄情况, 以及其是否容易降解或失活, 都需要进一步的实验研究和优化。针对不同HIV病毒株的广谱性和抗药性问题也需引起关注, 以确保该类化合物在面对病毒变异时仍能保持有效的抗病毒活性。最后, 临床试验的设计和开展也面临诸多挑战, 如患者的招募、试验方案的制定、伦理审查等环节均需严格规划和执行, 以获取可靠的临床数据, 验证其安全性和有效性。

因此, 对巴豆烷型二萜类化合物进行更深入的研究, 从而获得高效低毒、成药性更好的化合物。而随着交叉学科的不断深入, 将为其在新药研发中面临的问题提供解决方案, 这些问题的解决将为巴豆烷型二萜类化合物的临床应用奠定坚实的基础。

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References

[1] Wan H, Guo H, Liu X. Research progress on structure activity relationship of phorbol esters [J]. China Pharm (中国药业), 2013, 22: 95-96.

[2] Kulkosky J, Culnan DM, Roman J, et al. Prostratin: activation of latent HIV-1 expression suggests a potential inductive adjuvant therapy for HAART [J]. Blood, 2001, 98: 3006-3015.

[3] Tan HH, Xia M, Su P, et al. Research progress in tigliane-type macrocyclic diterpenoids [J]. China J Chin Mater Med (中国中药杂志), 2023, 48: 4620-4633.

[4] Hecker E, Bartsch H, Bresch H, et al. Structure and stereochemistry of the tetracyclic diterpene phorbol from *Croton tiglium* L. [J]. Tetrahedron Lett, 1967, 8: 3165-3170.

[5] Zhang XL, Wang L, Li F, et al. Cytotoxic phorbol esters of

Croton tiglium [J]. J Nat Prod, 2013, 76: 858-864.

[6] Bauer R, Tittel G, Wagner H. Isolation and detection of phorbolesters in crotonoil with HPLC. [J]. Planta Med, 1983, 48: 10-16.

[7] Kupchan SM, Uchida I, Branfman AR, et al. Antileukemic principles isolated from euphorbiaceae plants [J]. Science, 1976, 191: 571-572.

[8] El-Mekkawy S, Meselhy MR, Nakamura N, et al. Anti-HIV-1 phorbol esters from the seeds of *Croton tiglium* [J]. Phytochemistry, 2000, 53: 457-464.

[9] Jiang L, Zhang YB, Jiang SQ, et al. Phorbol ester-type diterpenoids from the twigs and leaves of *Croton tiglium* [J]. J Asian Nat Prod Res, 2017, 19: 1191-1197.

[10] Hecker E, Schmidt R. Phorbolesters—the irritants and cocarcinogens of *Croton tiglium* L. [J]. Fortschr Chem Org Naturst, 1974, 31: 377-467.

[11] Marshall GT, Kinghorn AD. Short-chain phorbol ester constituents of croton oil [J]. J Am Oil Chem Soc, 1984, 61: 1220-1225.

[12] Zhao BQ, Peng S, He WJ, et al. Antitubercular and cytotoxic tigliane-type diterpenoids from *Croton tiglium* [J]. Bioorg Med Chem Lett, 2016, 26: 4996-4999.

[13] Du QZ, Zhao YC, Liu HC, et al. Isolation and structure characterization of cytotoxic phorbol esters from the seeds of *Croton tiglium* [J]. Planta Med, 2017, 83: 1361-1367.

[14] Wang JF, Yang SH, Liu YQ, et al. Five new phorbol esters with cytotoxic and selective anti-inflammatory activites from *Croton tiglium* [J]. Bioorg Med Chem Lett, 2015, 25: 1986-1989.

[15] Ren FX, Ren FZ, Yang Y, et al. Tigliane diterpene esters from the leaves of *Croton tiglium* [J]. Helv Chim Acta, 2014, 97: 1014-1019.

[16] Zheng XX, Li L, Liu ZH, et al. Study on the quality evaluation of the leaves of *Croton tiglium* from different regions based on quality markers [J]. Phytochem Anal, 2024, 35: 817-824.

[17] Jiang ZY, Duan LK, Feng JE, et al. Bioactive constituents from the leaves of *Croton tiglium* [J]. Phytochem Lett, 2022, 49: 65-72.

[18] Li L, Zhao BQ, Zheng XX, et al. Diterpenoids with schistosomula-killing and anti-fibrosis activities *in vitro* from the leaves of *Croton tiglium* [J]. Molecules, 2024, 29: 401.

[19] Cong XY. Study on Terpenoids Constituents and Antiviral Activities of *Saussurea lappa* and *Croton tiglium* (云木香和巴豆中的萜类成分及其抗病毒活性研究)[D]. Kunming: Kunming University of Science and Technology, 2024.

[20] Zhang DD, Zhou B, Yu JH, et al. Cytotoxic tigliane-type diterpenoids from *Croton tiglium* [J]. Tetrahedron, 2015, 71: 9638-9644.

[21] Hu R, Huang JL, Yuan FY, et al. Crotonianoids A − C, three unusual tigliane diterpenoids from the seeds of *Croton tiglium* and their anti-prostate cancer activity [J]. J Org Chem, 2022, 87: 9301-9306.

[22] Zhang XL, Khan AA, Wang L, et al. Four new phorbol diesters from *Croton tiglium* and their cytotoxic activities [J]. Phytochem Lett, 2016, 16: 82-86.

[23] Zhang YP, Sui MH, Bai ZS, et al. Study on components with neuroinflammation inhibitory activities from *Croton tiglium* L. var. Xiaopadou [J]. Chem Biodivers, 2022, 19: e202200473.

[24] Wang JF, Qin L, Zhao BQ, et al. Crotonols A and B, two rare tigliane diterpenoid derivatives against K562 cells from *Croton tiglium* [J]. Org Biomol Chem, 2018, 17: 195-202.

[25] Li QR, Zhang XQ, Cui XJ, et al. Optimization preparation process of phorbol and synthesis, characterization and cytotoxicity of its derivatives [J]. Nat Prod Res Dev (天然产物研究与开发), 2019, 31: 1091-1100.

[26] Huang XL. Design, Synthesis and Biological Evaluation of Novel Phorbol Esters as Anti-HIV Agents (佛波醇衍生物的制备及其抗HIV活性研究)[D]. Suzhou: Soochow University, 2023.

[27] Li QR. Preparation and Biological Activity of Phorbol Derivatives (佛波醇衍生物的制备和活性研究)[D]. Suzhou: Soochow University, 2020.

[28] Bertolini TM, Giorgione J, Harvey DF, et al. Protein kinase C translocation by modified phorbol esters with functionalized lipophilic regions [J]. J Org Chem, 2003, 68: 5028-5036.

[29] El-Mekkawy S, Meselhy MR, Abdel-Hafez AA, et al. Inhibition of cytopathic effect of human immunodeficiency virus type-1 by various phorbol derivatives [J]. Chem Pharm Bull (Tokyo), 2002, 50: 523-529.

[30] Klausen TK, Pagani A, Minassi A, et al. Modulation of the transient receptor potential vanilloid channel TRPV4 by 4α-phorbol esters: a structure-activity study [J]. J Med Chem, 2009, 52: 2933-2939.

[31] Matsuya Y, Yu Z, Yamamoto N, et al. Synthesis of new phorbol derivatives having ethereal side chain and evaluation of their anti-HIV activity [J]. Bioorg Med Chem, 2005, 13: 4383-4388.

[32] Yamatsugu K, Motoki R, Kanai M, et al. Identification of potent, selective protein kinase C inhibitors based on a phorbol skeleton [J]. Chem Asian J, 2006, 1: 314-321.

[33] Huang XL, Huang XS, Li QR, et al. Seco-cyclic phorbol derivatives and their anti-HIV-1 activities [J]. Chin J Nat Med, 2024, 22: 365-374.

[34] Huang XL, Tang CR, Huang XS, et al. Synthesis and anti-HIV activities of phorbol derivatives [J]. Chin J Nat Med, 2024, 22: 146-160.

[35] Márquez N, Calzado MA, Sánchez-Duffhues G, et al. Differential effects of phorbol-13-monoesters on human immunodeficiency virus reactivation [J]. Biochem Pharmacol, 2008, 75: 1370-1380.

[36] Tostes JBF, Carvalho ALD, Ribeiro da Silva AJ, et al. Phorbol esters from the latex of *Euphorbia umbellata*: bioguided isolation of highly potent HIV-1 latency interrupters in virus reservoir cells [J]. J Nat Prod, 2021, 84: 1666-1670.

[37] Reuse S, Calao M, Kabeya K, et al. Synergistic activation of

HIV-1 expression by deacetylase inhibitors and prostratin: implications for treatment of latent infection [J]. PLoS One, 2009, 4: e6093.

[38] Gustafson KR, Cardellina JH 2nd, McMahon JB, et al. A nonpromoting phorbol from the samoan medicinal plant *Homalanthus nutans* inhibits cell killing by HIV-1 [J]. J Med Chem, 1992, 35: 1978-1986.

[39] Lee HK, Kim HS, Pyo M, et al. Phorbol ester activates human mesenchymal stem cells to inhibit B cells and ameliorate lupus symptoms in MRL. *Fas*^{lpr} mice [J]. Theranostics, 2020, 10: 10186-10199.

[40] Yang Y, Cong H, Han CC, et al. 12-Deoxyphorbol 13-palmitate inhibits the expression of VEGF and HIF-1α in MCF-7 cells by blocking the PI3K/Akt/mTOR signaling pathway [J]. Oncol Rep, 2015, 34: 1755-1760.

[41] Edwards MC, Taylor SE, Williamson EM, et al. New phorbol and deoxyphorbol esters: isolation and relative potencies in inducing platelet aggregation and erythema of skin [J]. Acta Pharmacol Toxicol (Copenh), 1983, 53: 177-187.

[42] Ahmed S, Kozma R, Lee J, et al. The cysteine-rich domain of human proteins, neuronal chimaerin, protein kinase C and diacylglycerol kinase binds zinc. Evidence for the involvement of a zinc-dependent structure in phorbol ester binding [J]. Biochem J, 1991, 280: 233-241.

[43] Goel G, Makkar HPS, Francis G, et al. Phorbol esters: structure, biological activity, and toxicity in animals [J]. Int J Toxicol, 2007, 26: 279-288.

[44] Handa SS, Kinghorn AD, Cordell GA, et al. Plant anticancer agents. XXII. Isolation of a phorbol diester and its delta 5, 6-7 beta-hydroperoxide derivative from *Ostodes paniculata* [J]. J Nat Prod, 1983, 46: 123-126.

[45] Wang HB, Wang XY, Liu LP, et al. Tigliane diterpenoids from the euphorbiaceae and thymelaeaceae families [J]. Chem Rev, 2015, 115: 2975-3011.

[46] Wender PA, Kee JM, Warrington JM. Practical synthesis of prostratin, DPP, and their analogs, adjuvant leads against latent HIV [J]. Science, 2008, 320: 649-652.

[47] Li QR, Cheng YY, Zhao L, et al. New phorbol ester derivatives as potent anti-HIV agents [J]. Bioorg Med Chem Lett, 2021, 50: 128319.

[48] Inoue M, Kishimoto A, Takai Y, et al. Studies on a cyclic nucleotide-independent protein kinase and its proenzyme in mammalian tissues. II. Proenzyme and its activation by calcium-dependent protease from rat brain [J]. J Biol Chem, 1977, 252: 7610-7616.

[49] Yang QL, Langston JC, Tang Y, et al. The role of tyrosine phosphorylation of protein kinase C delta in infection and inflammation [J]. Int J Mol Sci, 2019, 20: 1498.

[50] Mor-Vaknin N, Torgeman A, Galron D, et al. The long terminal repeats of human immunodeficiency virus type-1 and human T-cell leukemia virus type-I are activated by 12-*O*-tetradecanoylphorbol-13-acetate through different pathways [J]. Virology, 1997, 232: 337-344.

[51] Jabareen A, Suleman M, Abu-Jaafar A, et al. Different molecular mechanisms of HTLV-1 and HIV LTR activation by TPA [J]. Biochem Biophys Res Commun, 2018, 500: 538-543.

[52] Williams SA, Chen LF, Kwon H, et al. Prostratin antagonizes HIV latency by activating NF-kappaB [J]. J Biol Chem, 2004, 279: 42008-42017.

[53] Wang HP, Zhu XX, Zhu Y, et al. Protein kinase D3 is essential for prostratin-activated transcription of integrated HIV-1 provirus promoter *via* NF-κB signaling pathway [J]. Biomed Res Int, 2014, 2014: 968027.

[54] De la Torre-Tarazona HE, Jiménez R, Bueno P, et al. 4-Deoxyphorbol inhibits HIV-1 infection in synergism with antiretroviral drugs and reactivates viral reservoirs through PKC/MEK activation synergizing with vorinostat [J]. Biochem Pharmacol, 2020, 177: 113937.

[55] López-Huertas MR, Li J, Zafar A, et al. PKCθ and HIV-1 transcriptional regulator Tat co-exist at the LTR promoter in CD4(+) T cells [J]. Front Immunol, 2016, 7: 69.

[56] Hezareh M, Moukil MA, Szanto I, et al. Mechanisms of HIV receptor and co-receptor down-regulation by prostratin: role of conventional and novel PKC isoforms [J]. Antivir Chem Chemother, 2004, 15: 207-222.

[57] Chen H, Zhang R, Luo RH, et al. Anti-HIV activities and mechanism of 12-*O*-tricosanoylphorbol-20-acetate, a novel phorbol ester from *Ostodes katharinae* [J]. Molecules, 2017, 22: 1498.