Chemistry of Hypecoum Alkaloids

Subjects: Chemistry, Organic

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Genus *Hypecoum* Tourn. ex L. belongs to the poppy family Papaveraceae and comprises about 19 species occurring in Europe, Northern Africa and Asia. *Hypecoum* species have been widely used in traditional medicine as antipyretic, analgesic and anti-inflammatory remedies. The effects are associated with the biologically and pharmacologically active isoquinoline alkaloids in them such as protopines, protoberberines, benzophenanthridines, aporphines, simple isoquinolines, secoberbines, spirobenzylisoquinolines and others.

isoquinoline alkaloids *Hypecoum*

1. Introduction

The flowering plants of the genus *Hypecoum*, belonging to the family Papaveraceae, subfamily Fumarioideae, are widely distributed in temperate areas from Europe to Africa to Southwestern Asia. It is represented by 19 species (23 synonyms), with 2 accepted subspecies and 1 ambiguous name [1]. These plants have recognized medicinal value and are used in different forms of traditional medicine in the treatment and prevention of many diseases—colds, pneumonia, pharyngitis, inflamed red eyes, hepatitis, cholecystitis and other [2][3][4][5][6]. Scientific investigations of the *Hypecoum* species show that many of the therapeutic effects of the plants are primarily related to the bioactive isoquinoline alkaloids found in them. The known alkaloids in the genus belong to the various classes of isoquinolines—protopines, protoberberines, benzophenanthridines, aporphines, simple isoquinolines, secoberbines, spirobenzylisoquinolines and others. Protopine is a predominant alkaloid isolated from all investigated plants of the genus [2][7][8][9][10][11][12][13][14][15][16][17][18][19][20][21][22][23][24]. Besides being biologically active compounds, isoquinoline alkaloids are characteristic secondary metabolites in the family Papaveraceae and can be used for chemotaxonomic purposes [25].

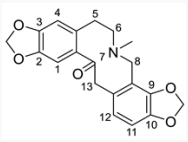
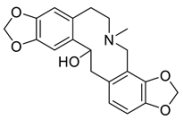
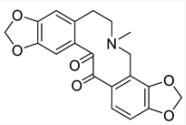
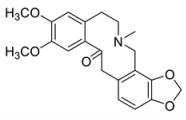
In recent years, more than 40 alkaloids have been identified in *Hypecoum* species, and new alkaloid structures, along with their pharmacological activities, are reported every year, enriching the diversity of natural compounds. Some of them have promising properties for the treatment of important diseases such as inflammation, cancer and microbial infections [18][19][22][23][26][27][28][29].

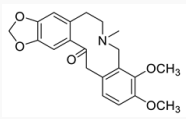
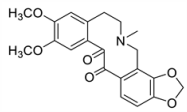
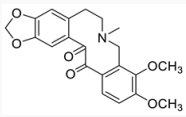
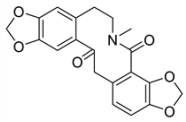
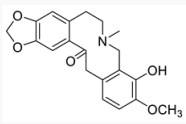
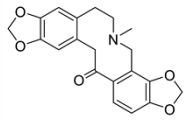
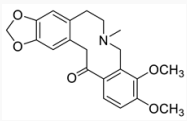
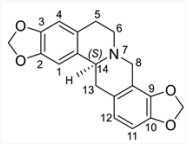
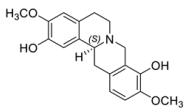
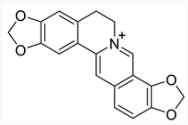
2. *Hypecoum* alkaloids

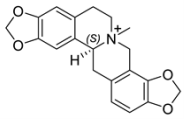
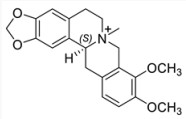
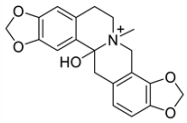
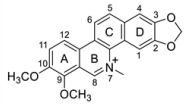
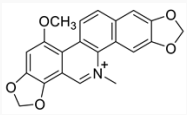
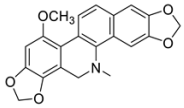
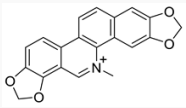
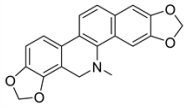
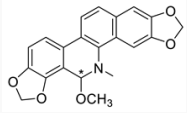
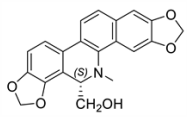
Alkaloids are a large group of *N*-containing natural compounds with diverse structures and a wide spectrum of pharmacological effects on human health. The *Hypecoum* species are recognized as important medicinal plants, biosynthesizing isoquinoline alkaloids as major active ingredients.

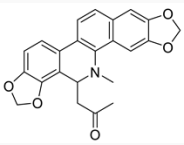
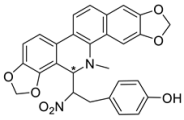
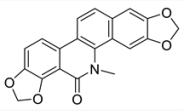
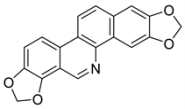
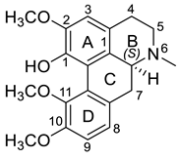
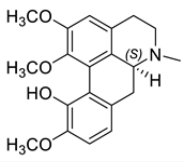
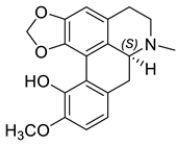
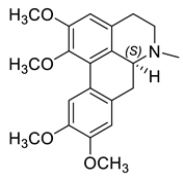
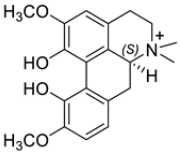
This section summarizes the alkaloid compounds that have been identified in the *Hypecoum* spp. since 1972 (**Table 1**) [2][7][8][9][10][11][12][13][14][15][16][17][18][19][20][21][22][23][24][27][30][31][32][33][34][35][36][37][38][39][40]. So far, a total of 86 naturally occurring alkaloids have been reported for ten plant species—*H. procumbens*, *H. procumbens* var. glaucescens, *H. imberbe*, *H. lactiflorum*, *H. pendulum*, *H. trilobum*, *H. leptocarpum*, *H. erectum*, *H. ponticum* and *H. parviflorum*. Based on their structures, the *Hypecoum* alkaloids can be divided into eight major groups: protopines (**1**–**11**), protoberberines (**12**–**17**), benzophenantridines (**18**–**28**), aporphines (**29**–**33**), simple isoquinolines (**34**–**38**), secoberbines (**39**–**66**), spirobenzilisoquinolines (**67**–**73**) and others (**74**–**86**). Two chemical structures have been detected in the literature with the name leptocarpine—protopine alkaloid **8** and alkaloid **82**. Both compounds have been identified in *H. leptocarpum* [10][22][32]. On the other hand, the structure of alkaloid **41** has been published in the literature under two different names, dihydroleptopine and coryximine, isolated from *H. leptocarpum* [22][23][33]. Similarly, the newly found in *H. erectum* 2-(1,3-dioxolo [4,5-h]isoquinolin-7-yl)-4,5-dimethoxy-N-methyl-benzenethanamine has the same structure as the alkaloid leptocarmine (**62**), isolated from *H. leptocarpum* [19][23][24].

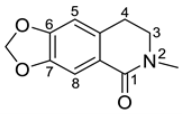
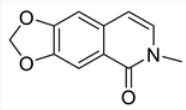
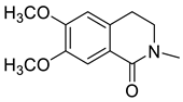
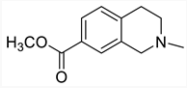
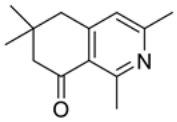
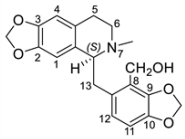
Table 1. Alkaloid structures reported for *Hypecoum* spp.

Alkaloids/Types	Structure	Species	References
Protopines			
Protopine (**1**)		*H. procumbens* *H. procumbens* var. *glaucescens* *H. imberbe* *H. lactiflorum* *H. pendulum* *H. trilobum* *H. leptocarpum* *H. erectum* *H. ponticum* *H. parviflorum*	[2][7][8][9][10][11][12][13][14][15][16][17][18][19][20][21][22][23][24]
Dihydroprotopine (**2**)		*H. procumbens* *H. imberbe* *H. leptocarpum*	[17][24]
13-Oxoprotopine (**3**)		*H. procumbens* *H. erectum*	[15][19]
Cryptopine (**4**)		*H. procumbens* var. *glaucescens* *H. erectum* *H. leptocarpum*	[2][11][13][19][20][21][22][23][30]

Alkaloids/Types	Structure	Species	References
Allocryptopine (**5**)		*H. lactiflorum* *H. leptocarpum* *H. procumbens* *H. procumbens* var. *glaucescens* *H. erectum*	[7][8][10][11][13][14][19][21][30][31]
13-Oxocryptopine (**6**)		*H. erectum*	[19]
13-Oxoallocryptopine (**7**)		*H. erectum*	[19]
Leptocarpine (**8**) *		*H. leptocarpum*	[32]
Hunnemanine (**9**)		*H. procumbens*	[15]
Bis[1,3]benzodioxolo[4,5-c:5′,6′-g]azecin-14(4*H*)-one, 5,6,7,13-tetrahydro-5-methyl-one (**10**)		*H. erectum*	[19]
6,7,8,14-Tetrahydro-3,4-dimethoxy-6-methylbenzo [c][1,3]benzodioxolo [5,6-g]azecin-15(5*H*)-one (**11**)		*H. erectum*	[19]
Protoberberines			
(*S*)-Stylopine (**12**)		*H. procumbens*	[17]
(*S*)-Scoulerine (**13**)		*H. procumbens*	[8][15]
Coptisine (**14**)		*H. procumbens* *H. leptocarpum* *H. erectum*	[8][14][20][23][30][31]

Alkaloids/Types	Structure	Species	References
(*S*)-*N*-Methylstylopine (**15**)		*H. lactiflorum* *H. procumbens* *H. ponticum*	[7][17][18]
(*S*)-*N*-Methylcanadine (**16**)		*H. lactiflorum* *H. erectum* *H. procumbens* *H. ponticum* *H. leptocarpum*	[7][13][17][18][21]
Hydroprotopine (**17**)		*H. leptocarpum*	[27]
Benzophenanthridines			
Chelerythrine (**18**)		*H. procumbens* *H. leptocarpum*	[8][14][30]
Chelirubine (**19**)		*H. procumbens*	[8][14]
Dihydrochelirubine (**20**)		*H. procumbens*	[17]
Sanguinarine (**21**)		*H. procumbens* *H. leptocarpum* *H. trilobum* *H. ponticum* , *H. imberbe*	[14][17][18][21][30]
Dihydrosanguinarine (**22**)		*H. imberbe* *H. leptocarpum* *H. procumbens*	[9][10][15]
(*R*,*S*)-8-Methoxydihydrosanguinarine (**23**)		*H. procumbens* *H. leptocarpum* *H. imberbe*	[8][9][10]
(*S*)-8-Hydroxymethyldihydrosanguinarine (**24**)		*H. erectum*	[19]

Alkaloids/Types	Structure	Species	References
8-Acetonyldihydrosanguinarine (**25**)		*H. procumbens* *H. leptocarpum*	[8][10]
(*R*,*S*)-Nitrotyrasanguinarine (**26**)		*H. imberbe* *H. pendulum* *H. procumbens*	[9]
Oxysanguinarine (**27**)		*H. procumbens*	[8][15]
Norsanguinarine (**28**)		*H. procumbens* *H. leptocarpum*	[8][15][23]
Aporphines			
(*S*)-Corydine (**29**)		*H. procumbens* *H. leptocarpum*	[30]
(*S*)-Isocorydine (**30**)		*H. procumbens* *H. procumbens* var. *glaucescens* *H. leptocarpum*	[8][11][30]
(*S*)-Bulbocapnine (**31**)		*H. imberbe*	[9]
(*S*)-Glaucine (**32**)		*H. procumbens*	[8]
(*S*)-Magnoflorine (**33**)		*H. procumbens* *H. leptocarpum*	[30]

Alkaloids/Types	Structure	Species	References
Simple isoquinolines			
Oxohydrastinine (**34**)		*H. imberbe* *H. leptocarpum* *H. erectum*	[2][9][10][12][13][19][21][22][23][24][27]
Doryanine (**35**)		*H. erectum*	[19]
N-Methylcorydaldine (**36**)		*H. erectum* *H. leptocarpum*	[13][19][23]
2-Methyl-1,2,3,4-tetrahydro isoquinoline-7-carboxylic acid methyl ester (**37**)		*H. erectum*	[19]
1,3,6,6-Tetramethyl-5,6,7,8-tetrahydroisoquiolin-8-one (**38**)		*H. erectum*	[19]
Secoberbines			
(*S*)-Corydalisol (**39**)		*H. procumbens*	[8]
(*S*)-*N*-Methylcorydalisol (**40**)	Diversity 15 01023 i040	*H. lactiflorum*	[7]
(*S*)-Dihydroleptopine (**41**) (Coryximine)	Diversity 15 01023 i041	*H. leptocarpum*	[22][23][33]
Hypecocarpinine (**42**)	Diversity 15 01023 i042	*H. leptocarpum*	[24]
Hypecocarpine (**43**)	Diversity 15 01023 i043	*H. leptocarpum*	[27]
Leptopinine (**44**)	Diversity 15 01023 i044	*H. leptocarpum*	[12]
Leptopine (**45**)	Diversity 15 01023 i045	*H. leptocarpum*	[12][21]
Leptopidine (**46**)	Diversity 15 01023 i046	*H. leptocarpum*	[12][21][22][23][24][27]

Alkaloids/Types	Structure	Species	References
Hypepontine (**47**)	 Diversity 15 01023 i047	*H. ponticum*	[17][18]
N-Methylcoryximine (**48**)	 Diversity 15 01023 i048	*H. pendulum*	[34]
Hendersine B (**49**)	 Diversity 15 01023 i049	*H. leptocarpum*	[23]
Procumbine (**50**)	 Diversity 15 01023 i050	*H. procumbens* *H. leptocarpum*	[30][35]
Leptopidinine (**51**)	 Diversity 15 01023 i051	*H. leptocarpum*	[12][21][22]
Torulosine (**52**)	 Diversity 15 01023 i052	*H. leptocarpum*	[23][33]
8-Oxohypecorinine *N*-oxide (**53**)	 Diversity 15 01023 i053	*H. leptocarpum*	[33]
N-Methyldemethyltorulosine (**54**)	 Diversity 15 01023 i054	*H. leptocarpum*	[23][33]
(*R*,*S*)-Hypecorinine (**55**)	 Diversity 15 01023 i055	*H. procumbens* *H. procumbens* var. *glaucescens* *H. erectum*	[8][11][13][14][19][31][36]
(*R*,*S*)-8-Oxohypecorinine (**56**)	 Diversity 15 01023 i056	*H. procumbens* var. *glaucescens*	[11]
Hypecorine (**57**)	 Diversity 15 01023 i057	*H. erectum*	[14][31][36]
2,3-Dimethoxyhypecorinine (**58**)	 Diversity 15 01023 i058	*H. erectum*	[19]
(*S*)-Peshawarine (**59**)	 Diversity 15 01023 i059	*H. parviflorum*	[8][16]
Corydamine (**60**)	 Diversity 15 01023 i060	*H. leptocarpum* *H. erectum*	[10][19][22][23][24][31]
Corydamine acid (**61**)	 Diversity 15 01023 i061	*H. leptocarpum*	[23]
Leptocaramine (**62**) (2-(1,3-dioxolo [4,5-*h*]	 Diversity 15 01023 i062	*H. leptocarpum* *H. erectum*	[19][23][24]

[42]

2.5. Simple Isoquinoline Alkaloids

Alkaloids/Types	Structure	Species	References
isoquinolin-7-yl)-4,5-dimethoxy-*N*-methyl-benzeneethanamine)			
N-Formylcorydamine (**63**)	 Diversity 15 01023 i063	*H. erectum* *H. procumbens*	[15][19]
2,3-Dimethoxy-*N*-formyl corydamine (**64**)	 Diversity 15 01023 i064	*H. erectum*	[19]
Hypecumine (**65**)	 Diversity 15 01023 i065	*H. procumbens*	[15]
7-*N*-Methyl-7-*N*-oxide-2,3-di-methoxycorydamine (**66**)	 Diversity 15 01023 i066	*H. erectum*	[19]
Spirobenzylisoquinolines			
(*S*,*S*)-Hyperectumine B (**67**)	 Diversity 15 01023 i067	*H. erectum*	[19]
(*S*,*S*)-2,3-Dimethoxyhyperectumine B (**68**)	 Diversity 15 01023 i068	*H. erectum*	[19]
(*R*,*S*) and (*S*,*R*)-2,3-Dimethoxyhyperectine (**69**)	 Diversity 15 01023 i069	*H. erectum*	[19]
(*R*,*S*) and (*S*,*R*)-Hyperectine (**70**)	 Diversity 15 01023 i070	*H. leptocarpum* *H. erectum*	[10][19][31][36][37]
(*S*,*S*) and (*R*,*R*)-Isohyperectine (**71**)	 Diversity 15 01023 i071	*H. leptocarpum* *H. erectum*	[10][12][37]
(*R*,*R*)-Sibiricine (**72**)	 Diversity 15 01023 i072	*H. erectum*	[19]
(*R*,*S*)-Hypecoleptopine (**73**)	 Diversity 15 01023 i073	*H. erectum* *H. leptocarpum*	[21][33][38]
Other alkaloids			
(*S*)-*N*-Methylcoclaurine (**74**)	 Diversity 15 01023 i074	*H. procumbens*	[17]
N-Methylsecoglaucine (**75**)	 Diversity 15 01023 i075	*H. ponticum*	[17][18]
(*R*)-Turkiyenine (**76**)	 Diversity 15 01023 i076	*H. procumbens* *H. pendulum* *H. imberbe*	[9][15][39][40]

This group summarizes the *Hypecoum* alkaloids of various structural types (**74**–**86**) such as the benzylisoquinoline—*N*-methylcoclaurine (**74**), the phenantrene—*N*-methylsecoglaucine (**75**), the indenobenzazepines (**80**, **81**), the phthalideisoquinoline—hypecoumine (**83**), the C_{19}-benzylisoquinoline—hyperectumine (**84**) and alkaloids with unusual structures that cannot be assigned to any of the established groups (**76**–**79**, **82**, **85**, **86**) (**Table 1**). The alkaloids **80**, **81** and **84** have shown significant anti-inflammatory properties in different in vitro models [19].

Alkaloids/Types	Structure	Species	References
(*S*)-Oxoturkiyenine (**77**)	Diversity 15 01023 i077	*H. pendulum*	[39]
Leptocarpinine (**78**)	Diversity 15 01023 i078	*H. leptocarpum*	[12]
Leptocarpinine B (**79**)	Diversity 15 01023 i079	*H. leptocarpum*	[23]
(*S*,*S*)-*Trans*-benzindenoazepines (**80**)	Diversity 15 01023 i080	*H. erectum*	[19]
(*S*,*S*)-*O*-Methylfumarostelline (**81**)	Diversity 15 01023 i081	*H. erectum*	[19]
Leptocarpine (**82**) *	Diversity 15 01023 i082	*H. leptocarpum*	[10][22]
*Hypecoum*ine (**83**)	Diversity 15 01023 i083	*H. procumbens*	[2]
Hyperectumine (**84**) (8*S*, 9*R*, 15*R*) (8*R*, 9*S*, 15*S*)	Diversity 15 01023 i084	*H. erectum*	[25]
Dibenzooxazacycloundecine (**85**)	Diversity 15 01023 i085	*H. erectum*	[19]
Hypeisoxazole A (**86**) (6*S*, 8*R*, 14*R*) (6*R*, 8*S*, 14*S*)	Diversity 15 01023 i086	*H. erectum*	[38]

* Two chemical structures with the name leptocarpine (**8**, **82**).

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