Chemoinformatic analysis of alkaloids isolated from *Peganum* genus

Omer Bayazeid (omerbayazid@gmail.com)
Hacettepe Universitesi https://orcid.org/0000-0002-2638-8475
Tohfa Nasibova
Azerbaijan Medical University

Research Article

Keywords: Peganum , Alkaloids, Neuroactivity, Phytochemistry, Traditional usage

Posted Date: April 13th, 2021

DOI: https://doi.org/10.21203/rs.3.rs-387620/v1

Abstract

Peganum genus is rich with its high phytochemical and botanical variability. *Peganum* species have been used as sedative, antitumor, analgesics, antidepressant, and other medicinal purposes. The aim of this research is to study the molecular diversity of *Peganum* genus to shed more lights on the structure-activity relationship of the alkaloids isolated from *Peganum* genus. All *Peganum* alkaloids were grouped according to their structure properties. A chemoinformatic approach (Swiss Model) was used to determine the molecular targets of these alkaloids. To visualize the results, R programming language was used to generate hierarchical clustering heatmaps. The results of this study helps researcher to better understanding of the structural-activity relationship of *Peganum* alkaloids.

Introduction

Peganum genus belongs to Zygophyllaceae family and it has six species including *P. harmala* L., *P. nigellastrum* Bunge, *P. multisectum* (Maxim.) Bobrov and *P. mexicanum* Gray [1]. *P. harmala* (also known as Harmal or Syrian rue) has a wider distribution area, and its found in Asia, North Africa, America and Australia. Other species grow in specific regions such as *P. nigellastrum* and *P. multisectum* Central, and they are found in Asia, Mongolia, China. *P. mexicanum* is found mainly in Mexico [2, 3]. *Peganum* species are categorized according to their morphological characteristics (such as seed shape, seed coat features, leaves, and petal color), as well as genetic and cytological differences. *Peganum genus* is widely used in traditional medicine, it's used as carminative, emetic, analgesic, aphrodisiac and also to treat epilepsy and memory loss [4]. The traditional usages of *Peganum* species are available in Table 1.

Table 1
Traditional usage of *Peganum* species.

Species	Part used	Traditional usage
Peganum harmala	Seeds	Hypertension, thrombosis, constipation, metereoism, diarrhea, pain (intestinal, rheumatic, headache, toothache, back pain), memory loss, depression, abortion, stimulation of menstruation, subcutaneous tumors, bacterial, fungal, viral infections, diabetes mellitus, healing wound, Fever, dermatosis, ulcer, malaria, asthma, bronchitis, expectoration, cough, kidney stone, eye complaints, syphilis [3, 5–11].
Peganum nigellastrum	whole plants or seeds	Rheumatism, irregular menstruation, cough, asthma, abscesses, inflammatory diseases [12]

The effect of *P. harmala* is a well-documented in Iran, Turkey, Mongolia and Chinese region; Xinjiang [13]. The bioactivities of *P. harmala* have been well-studied, for this reason, *P. harmala* is widely used in folk medicine. All biological activities related to *Peganum* specie can be found in Table 2. *Peganum* alkaloids in this study are grouped into four main groups: β-**carboline alkaloids** (harmine, harmaline and harmol),

indole alkaloids (6-methoxyindoline and Peganine A, B), **quinazoline alkaloids** (vasicin and vasicinone) and **quinoline alkaloids** (Ipidacrine).

Table 2
Biological activities of *Peganum* species.

Species	Part used	Biological activity
Peganum harmala	Seeds	Acetyl- and butyrylcholinesterase inhibitor [14], adrenergic receptor inhibitor [15], analgesic [8].
	Seeds, roots	MAO-A inhibitor [16], COMT inhibitor [17], human DNA topoisomerase I inhibitor [18].
	Seeds, leaves	antibacterial [19], antitumor [20], antiproliferative [21], antioxidant [22], anti-inflammatory [23], RNA- and DNA-binding [24].
Peganum nigellastrum	Seeds	Anti-Alzheimer [25], acetylcholinesterase inhibitor [12], butyrylcholinesterase inhibitor [26], antitumor activity [12], cytotoxic activity, inhibitory activity against topoisomerase I and II [27, 28], antiviral [12].
Peganum multisectum	Seeds	Antitumor activity [29], acetylcholinesterase inhibitor [12] [30], butyrylcholinesterase inhibitor [26].

Tryptamine is a major precursor of a wide range of β-carboline alkaloids [31] (Fig. 1). Tryptamine is formed from L-tryptophan by tryptophan decarboxylase. Indole alkaloids are also derived from the aromatic amino acid L-tryptophan which is produced through the shikimate pathway. On the other hand, quinazoline alkaloids can either be derived from L-asparagine (shown in Fig. 1) or from L-ornithine (not shown). Anthranilic acid forms the α part of quinazoline alkaloids and anthranoylphenylalanine forms the β part of quinazoline alkaloid [32].

Chemoinformatics is an area that deal indexing, collecting, and using information to better understand chemical compounds. Here we used of chemoinformatics techniques (Swiss model) to predict the molecular targets of *Peganum* alkaloids. Swiss model predicts most possible molecular targets for the small molecules based on shape similarity. The target estimation is based on 2D and 3D similarity of the small molecules using a library of 370,000 recognized molecules [33, 34]. We then used R programming language for data visualization to generate heatmaps to identify any pattern in the predicted data.

Result And Discussion

We have labeled unnamed alkaloids to improve the readability of the data analysis in the heatmaps. Table 3 lists the new labels assigned to each alkaloid.

Table 3
Compounds associated labels.

Compound name	Associated Label
2-Aldehyde-tetrahydroharmine	Compound I
3,4-dihydro-β-carboline	Compound II
6-Methoxytetrahydro-1-norharmanone	Compound III
1-ethyl-7-methoxy-9H-pyrido[3,4-b]indole	Compound IV
2-(indol-3-yl)ethyl-α-L-rhamnopyranosyl-(1 → 6)-β-D-glucopyranoside	Compound V
2-(indol-3-yl)ethyl-β-D-glucopyranoside	Compound VI
10-methyl-11-acetylvasicine	Compound VII
2-carboxyl-3,4-dihydroquinazoline	Compound VIII
2-deoxypeganylacetic acid	Compound IX
Vasicine-β-d-glucopyranosyl-(1→6)-β-d-glucopyranoside	Compound X
3-(4-Hydroxyphenyl)quinoline	Compound XI
3-(1H-indol-3-yl)quinoline	Compound XII
3-phenylquinoline	Compound XIII
4-amino-2-ethyl-3 methylquinoline	Compound XIV

β -carboline alkaloids

β-carboline alkaloids are a wide group of natural and synthetic alkaloids with a tricyclic pyrido[3,4-b]indole ring structure. They are characterized as a combination of indole structure and a pyridine ring. *β*-carboline alkaloids possess strong neuroactivity by targeting 5-hydroxytryptamine receptors, monoamine oxidase (MAO), N-Methyl-D-aspartic acid receptors, and dopaminergic signaling pathways [35]. *β*-carboline alkaloids have also been reported as inhibitors of DYRK1A kinase activity [36]. Some carboline derivatives have also been reported to act as Serine/threonine-protein kinase PLK1 [37] and CDK inhibitors [38]. Swiss predicted that the carbonyl substitution (R-C = O-R) at position 1 of *β*-carboline alkaloids (Compound III; 6-methoxytetrahydro-1-norharmanone and harmalacidine) increases the inhibitory effect of MAP kinase activated protein kinases. *β*-carboline alkaloids are potent dual specificity tyrosine-phosphorylation-regulated kinase 1A (DYRK1A) inhibitors, e.g. harmol has a half maximal inhibitory concentration (IC_{50}) of 90 nM [39]. Nevertheless, substitution can play a major role in increasing or diminishing the DYRK1A inhibitory effect of *β*-carboline alkaloid. Position 1 should always be substituted with only one group (it can be methyl or carbonyl). Adding hydroxyl or methoxy group to either position 6 or 7 can increase the activity dramatically especially in the methoxy group (Figs. 2 and

3). Inhibiting DYRK1A leads to a reduction in the phosphorylation of microtubule-associated protein tau [40]. Swiss predicted that *β*-carboline alkaloids that can inhibit DYRK1A (with high swiss score) are able to target microtubule-associated protein tau e.g. tetrahydroharmine (Fig. 2).

β-carboline alkaloids can be grouped into three main groups according to the saturation of the nitrogen-containing ring; fully aromatic *β*-carbolines, dihydro-*β*-carbolines (partially saturated ring) and tetrahydro-*β*-carbolines (completely saturated ring) [35]. Swiss predicted that only fully aromatic *β* -carbolines has the ability to inhibit MAO-A and B. The methoxy substitution at position 7 is important for activity as this part of the *β*-carboline alkaloid is expected to interact with the hydrophobic pocket of MAO [41]. Serotonin (5-HT) receptors consist of seven families and more the 15 subfamilies. Selectivity is a major problem when targeting 5-HT receptor. 5-HT (indolealkylamine) binds to all 5-HT receptors at a nanomolar level. The term semiselective agents' concept was created to distinguish molecules that have more selectivity (selective for two or three 5-HT subfamilies) than those who can bind to all 5-HT receptors. 5-HT subfamily specificity does not depend on specific chemical class, it mainly depends on the substituent type in the same chemical. This means that any small structural changes can lead to a great change in the selectivity [42]. Tetrahydro-*β*-carbolines is the class of *β*-carbolines alkaloids with the least selectivity toward 5-HT receptor subfamilies. The selectivity of tetrahydro-*β*-carbolines can be enhanced if it was position 1 is substituted with carbonyl group (compound III) or the nitrogen at position 2 is substituted with an aldehyde -CHO (compound I; 2-aldehyde-tetrahydroharmine). Dihydro-β-carbolines can be also less selective if they do not have any substitution (compound II; 3,4-dihydro-β-carboline) (Fig. 2). All fully aromatic *β*-carbolines such as harmine have high swiss score (better activity) and better selectivity (Fig. 3).

Indole alkaloids

Indole alkaloids are bicyclic alkaloids that have benzene ring connected to a five-membered pyrrole ring. The nitrogen atom in the pyrrole ring is behind the pharmacologically properties of indole alkaloids [38]. Indole alkaloids have been reported to have antinociceptive, antioxidant, anti-inflammatory, antitumor and antimicrobial properties as well as anti-butyrylcolinesterase and anti-acetylcholinesterase properties. They are frequently linked to G-protein receptor function, especially neuronal signal transmission through 5-HT/hydroxytryptamine receptors [43]. Compound VII (2-acetyl-3-(2-acetamidoethyl)-7-methoxyindole) and pegaharmaline F are very similar to melatonin structure (**Figure 4**). Melatonin is a cytoprotective agent and it stimulates the immune system to regulate the sleep/wake cycle. The pyrrole-ring in the melatonin is cleavage by the liver to produce N1-acetyl-N2-formyl-5-methoxykynuramine. This secondary metabolite supports mitochondrial function and act as neuroprotection [44]. Compound VII and pegaharmaline F are the only indole alkaloids that swiss predicted to interact with melatonin receptor 1A and 1B. In addition, they are the only indole alkaloids that can inhibit DYRK1A. *Peganum* indole alkaloids possess opioid receptor activity by target mu, delta and kappa-type opioid receptor. Swiss predicted that peganumaline A (dimeric form of peganumaline B) has the strongest mu, delta and kappa-type opioid receptor activity among other *Peganum* indole alkaloids (**Figure 4**). This is due to high 2D similarity between peganumaline A and 3-spirocyclic indolin-2-ones (CHEMBL381429). CHEMBL381429 binds with

kappa-type opioid receptor with IC_{50} of 1.2 μM [45]. Swiss predicted that *Peganum* indole alkaloids have a weak MAO and acetylcholinesterase activity.

Quinazoline alkaloids

Quinazoline alkaloids have a bicyclic structure that consists of two fused six-membered aromatic rings, a benzene ring, and a pyrimidine ring. These alkaloids are especially distinguished for their antimalarial and anticancer properties [46]. In addition, they also act as bronchodilator, antitussive, cytotoxic, antimycobacterial, antileishmanial and antiulcer effects [47]. Swiss predicted that *Peganum* quinazoline alkaloids possess weak serotonergic activity but some quinazoline alkaloids could possess potent cholinesterase activity. Substitution of quinazoline alkaloids have a big impact on its biological activities. Swiss predicted that quinazoline alkaloid with huge structure e.g. dimers (dipegine and dipeginol) and glucosides (vasicinol-Glu and vasicine-Glu) do not have cholinesterase activity as well as quinazoline alkaloid that lacks the five-member ring (compound VIII; 2-carboxyl-3,4-dihydroquinazoline) (**Figure 5**). Swiss predicted that both desoxypeganine and its derivative vasicine (hydroxy group at position 3) have very high cholinesterase activity. It has been reported that desoxypeganine inhibits acetylcholinesterase with IC_{50} of 3.72 μM [48] and vaccine inhibits butyrylcholinesterase with a IC_{50} of 3.13 μM [49]. Changing the position of the hydroxyl group (peganol) or adding a second hydroxyl group to desoxypeganine (vasicinol and 4-vasicinol) decrease the cholinesterase activity of quinazoline alkaloids.

Quinoline alkaloids

Quinoline alkaloids are derived from either anthranilic acid or tryptophan. Most of quinoline alkaloids are substituted at position 2 of the heterocycle [48]. Swiss predicted that some of *Peganum* quinoline alkaloids have kinase activity and some have cholinesterase activity. Ipidacrine has the strongest cholinesterase activity and it's probably due the additional five-member ring and the amine substitution, ipidacrine inhibits cholinesterase with IC_{50} of 70 nM [50]. Swiss also predicted that compound XII (3-(1H-indol-3-yl)quinoline) can target platelet derived growth factor receptor tyrosine kinase (PDGF) (high score) and epidermal growth factor receptor (EGFR) (low score). It has been reported that compound XII inhibits PDGF with IC_{50} of 8 μM and EGFR with IC_{50} of 20 μM [51]. In addition, quinoline alkaloids with phenol ring such as compound XI (3-(4-Hydroxyphenyl)quinoline) has mild mitogen-activated protein kinases activity and this is due to its high similarity with CHEMBL248643 which can inhibit mitogen-activated protein kinase p38 with IC_{50} of 20 μM and c-Jun N-terminal kinase 3 with IC_{50} of 0.59 μM [52, 53].

Conclusion

In conclusion, these research-based findings include an overview of *Peganum* genus phytochemical and bioactivity data. The molecular targets of alkaloids were predicted using chemoinformatic approach, which shed light on the structure-activity relationship of alkaloids isolated from *Peganum* species.

Declarations

Funding: N/A

Conflicts of interest/Competing interests: N/A

Availability of data and material: N/A

Code availability: N/A

Ethics approval: N/A

Consent to participate: N/A

Consent for publication: N/A

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Figures

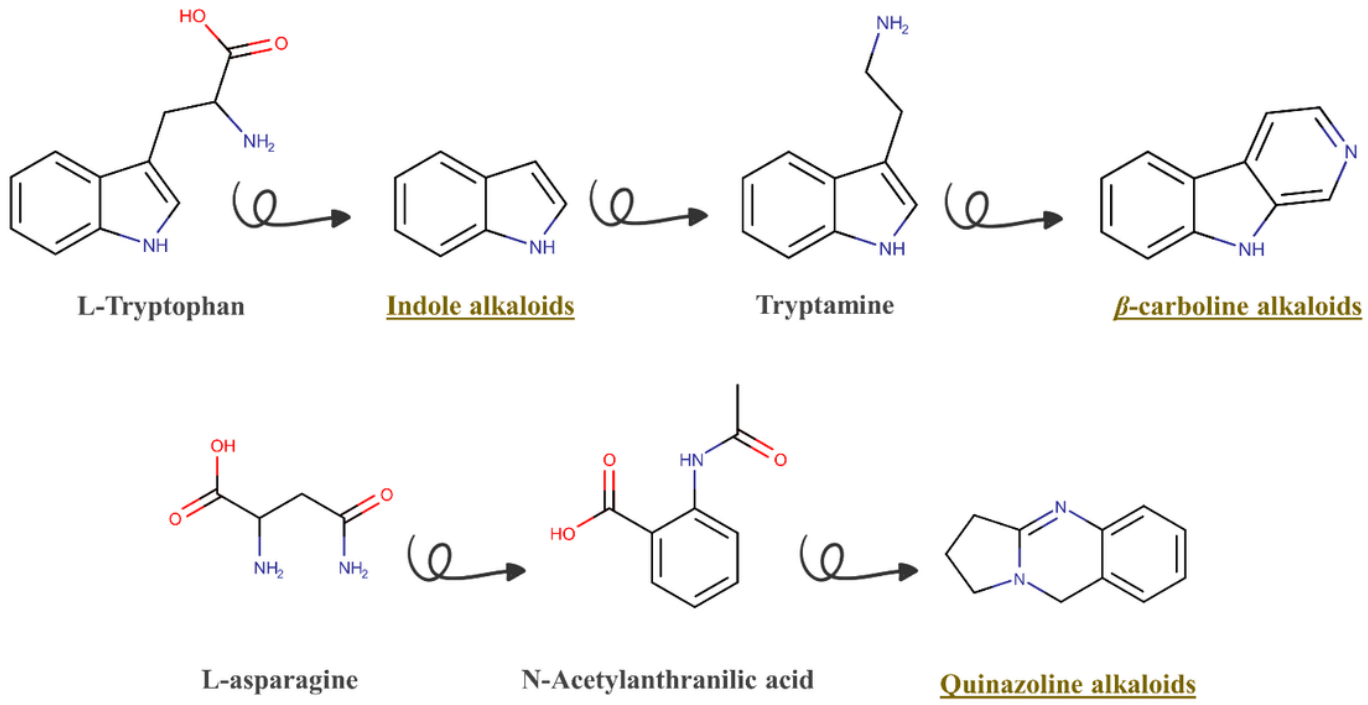

Figure 1

Biosynthetic pathway of Peganum alkaloids.

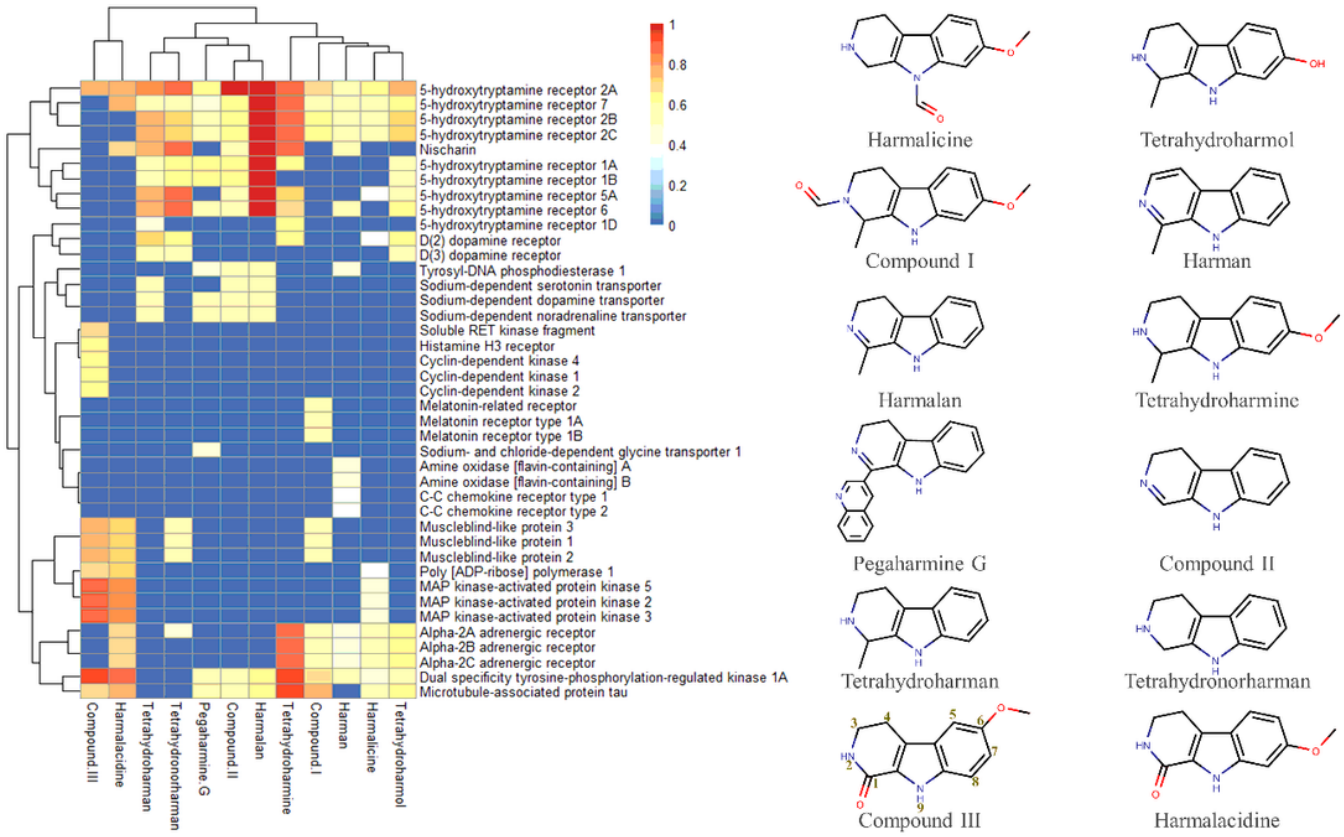

Figure 2

Consensus molecular targets of β-carboline alkaloids isolated from Peganum genus (Part I).

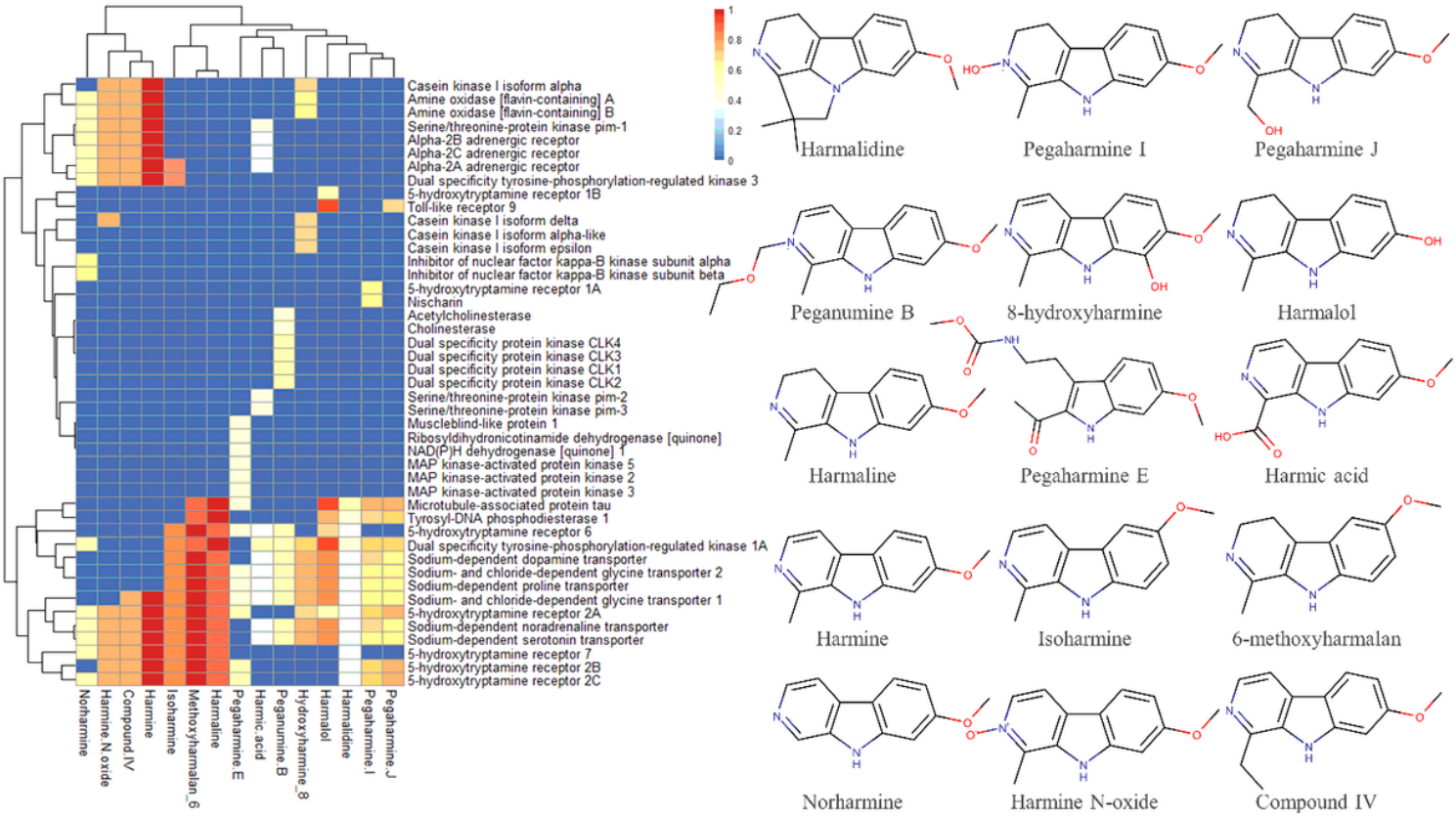

Figure 3

Consensus molecular targets of β-carboline alkaloids isolated from Peganum genus (Part II).

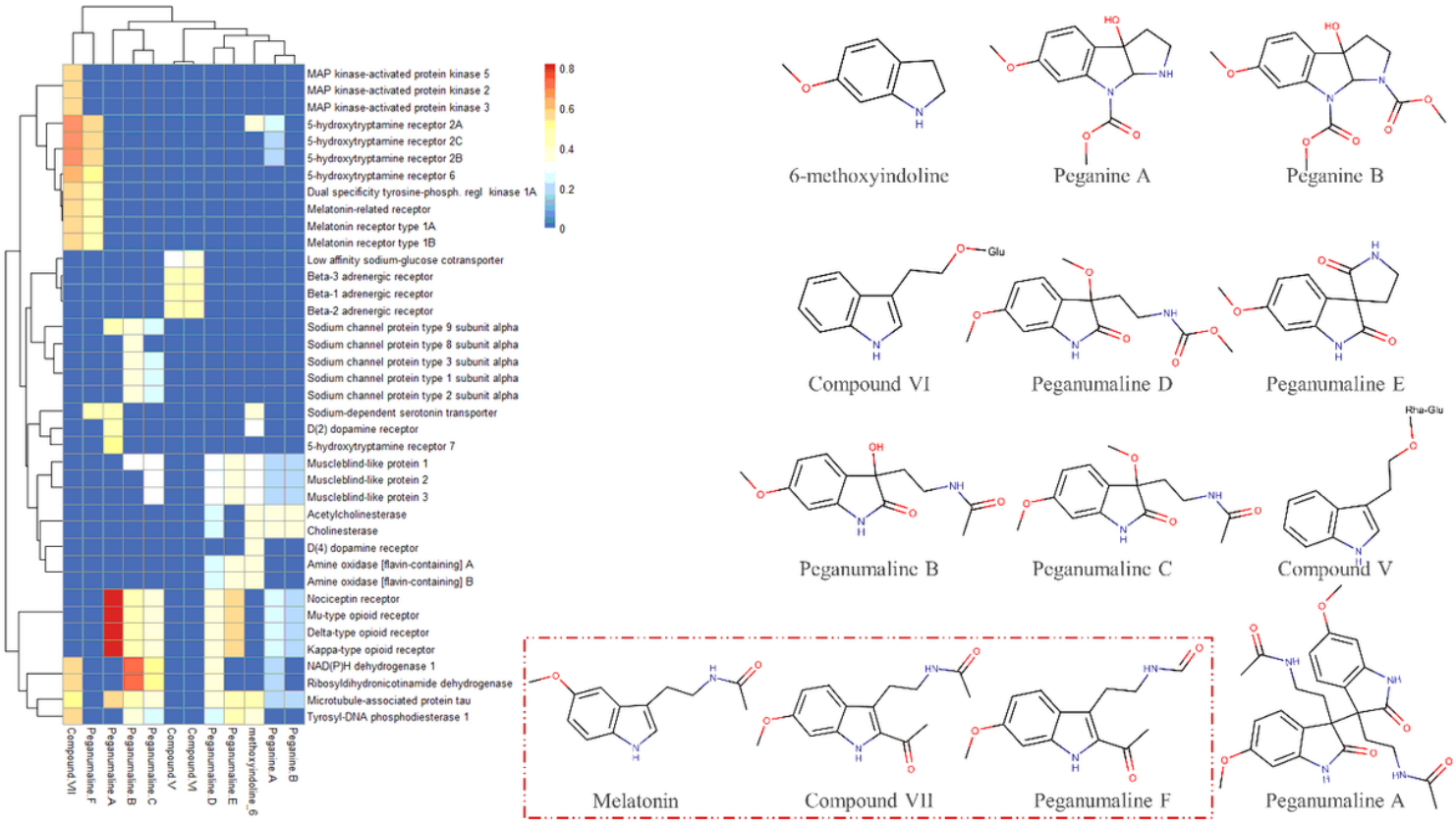

Figure 4

Consensus molecular targets of indole alkaloids isolated from Peganum genus.

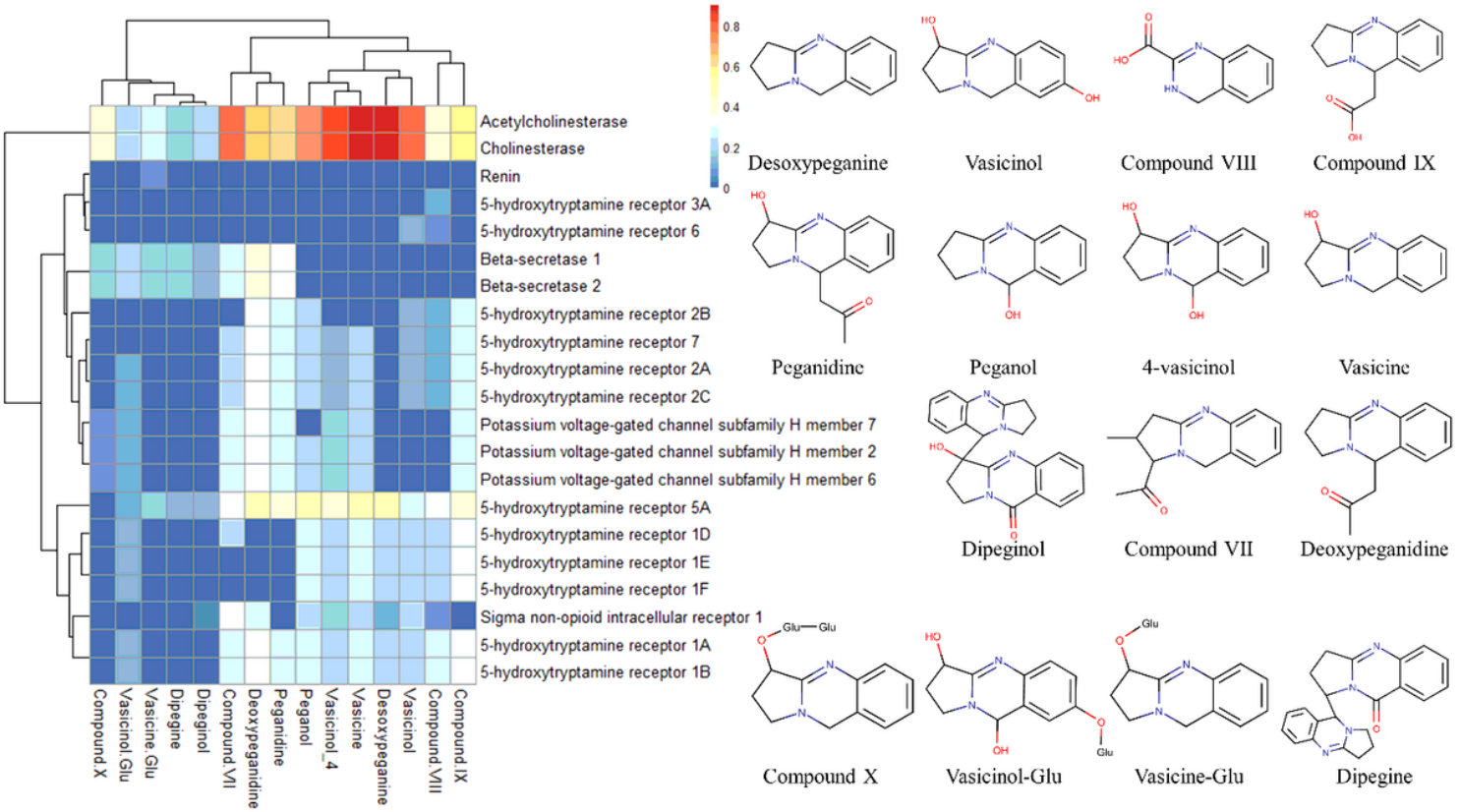

Figure 5

Consensus molecular targets of quinazoline alkaloids isolated from Peganum genus.

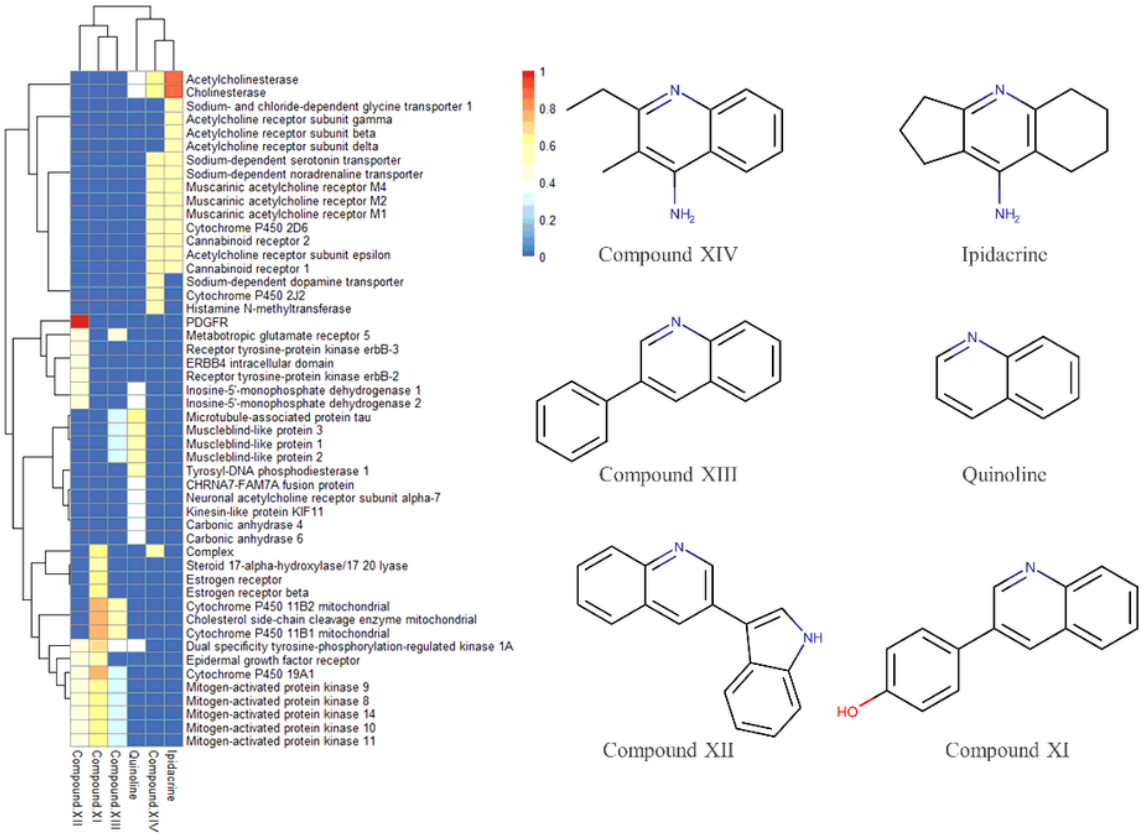

Figure 6

Consensus molecular targets of quinoline alkaloids isolated from Peganum genus.