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Maculine: a furoquinoline alkaloid from the family *Rutaceae*: sources, syntheses and biological activities

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This paper is dedicated to Prof Jan Bergman for his 80th birthday and his involvement in organic chemistry, and with deep appreciation for over 40 years of friendship

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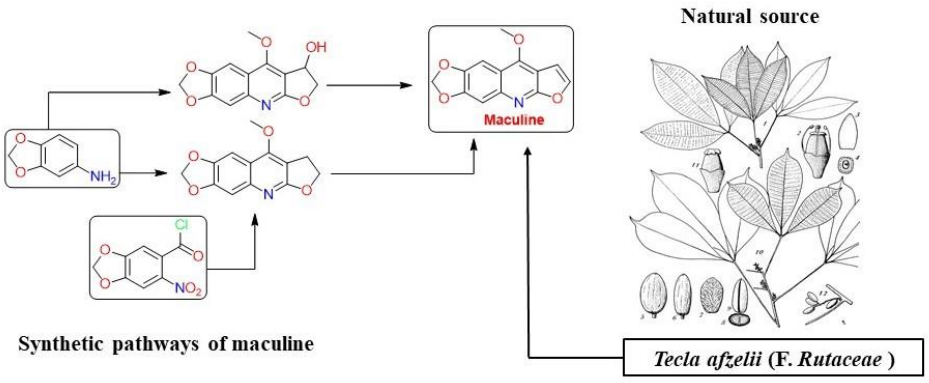
Abstract

Maculine is one of the furoquinolines which are characteristic of the family *Rutaceae*. Its chemical name is 9-methoxy[1,3]dioxolo[4,5-*g*]furo[2,3-*b*]quinoline and it was isolated from several genera of *Rutaceae*. The present mini-review covers the different sources of maculine, its methods of separation, synthetic pathways and biological activities.



Keywords: Maculine, furoquinoline, *Rutaceae*, alkaloids

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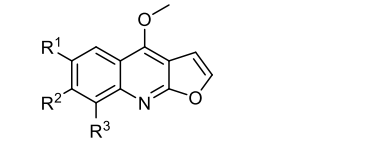
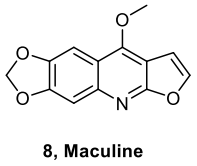
1. Introduction

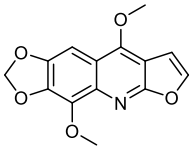
The Rutaceae family has about 140 genera,[1–4] consisting of herbs, shrubs and small trees which grow in all parts of the world, Moluccas, New Guinea, Australia, New Caledonia, Brazil, Cameroon. They are used in traditional medicine for treating snake bites, stomatitis, rheumatism, bronchitis and other diseases.[5–8] Rutaceae plant is the source of furoquinoline alkaloids, besides furanocoumarin alkaloids, phenolic-structured compounds and terpenes.[9–11] The main furoquinoline alkaloid compounds isolated from this family are dictamnine (**1**), skimmianine (**2**), γ-fagarine (**3**), haplopine (**4**), 7-hydroxydictamine (**5**), evolitrine (**6**), maculosidine (**7**), maculine (**8**), flindersiamine (**9**), tecleaverdoornine (**10**), leptanoine A (**11**), leptanoine B (**12**), leptanoine C (**13**), melineurine (**14**), kokusaginine (**15**), acronycidine (**16**), tecleamaniensine A (**17**), tecleamaniensine B (**18**), acronydine (**19**), isohaplopine (**20**), 5-(1,1-dimethylallyl)-8-hydroxyfuro[2,3-*b*]quinolone (**21**), isodictamnine (**22**), isomaculosidine (**23**), iso-γ-fagarine (**24**), dictangustine A (**25**), isopteleine (**26**), isoskimmianine (**27**), isokokusaginine (**28**), (+) isoplatydesmine (**29**), (+)-araliopsine (**30**), balfourodine (**31**), pseudobalfourodine (**32**), dihydroisodictamnine (**33**), dihydrodictamnine (**34**), evoxine (**35**) and isoevoxine (**36**).[12–17] (Figure 1) Many of these compounds have antifungal, anti-bacterial, anti-Alzheimer, anti-plasmodial and phototoxic properties.[18–22] Some of the others represent a promising perspective of being potential drugs. For example, it was reported that skimmianine (**2**), and melineurine (**12**) could potentially be used in the future to treat Alzheimer's disease.[8,22] In addition, Schimmer and Häfele



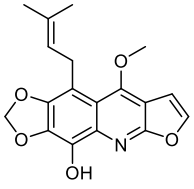
1, R^1=R^2=R^3=H, **Dictamnine**
2, R^1=H, R^2=R^3=OCH_3, **Skimmianine**
3, R^1=R^2=H, R^3=OCH_3, **γ-fagarine**
4, R^1=H, R^2=OH, R^3=OCH_3, **Haplopine**
5, R^1=R^3=H, R^2=OH, **7-Hydroxydictamnine**
6, R^1=R^3=H, R^2=OCH_3, **Evolitrine**
7, R^1=R^3=OCH_3, R^2=H, **Maculosidine**



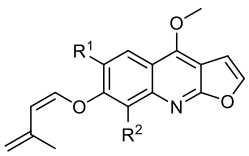
8, Maculine



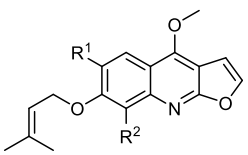
9, Flindersiamine



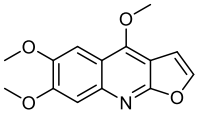
10, Tecleaverdoornine



11, R^1=R^2=H, **Leptanoine A**
12, R^1=OCH_3, R^2=H, **Leptanoine B**



13, R^1=OCH_3, R^2=H, **Leptanoine C**
14, R^1=R^2=H, **Melineurine**



15, Kokusaginine

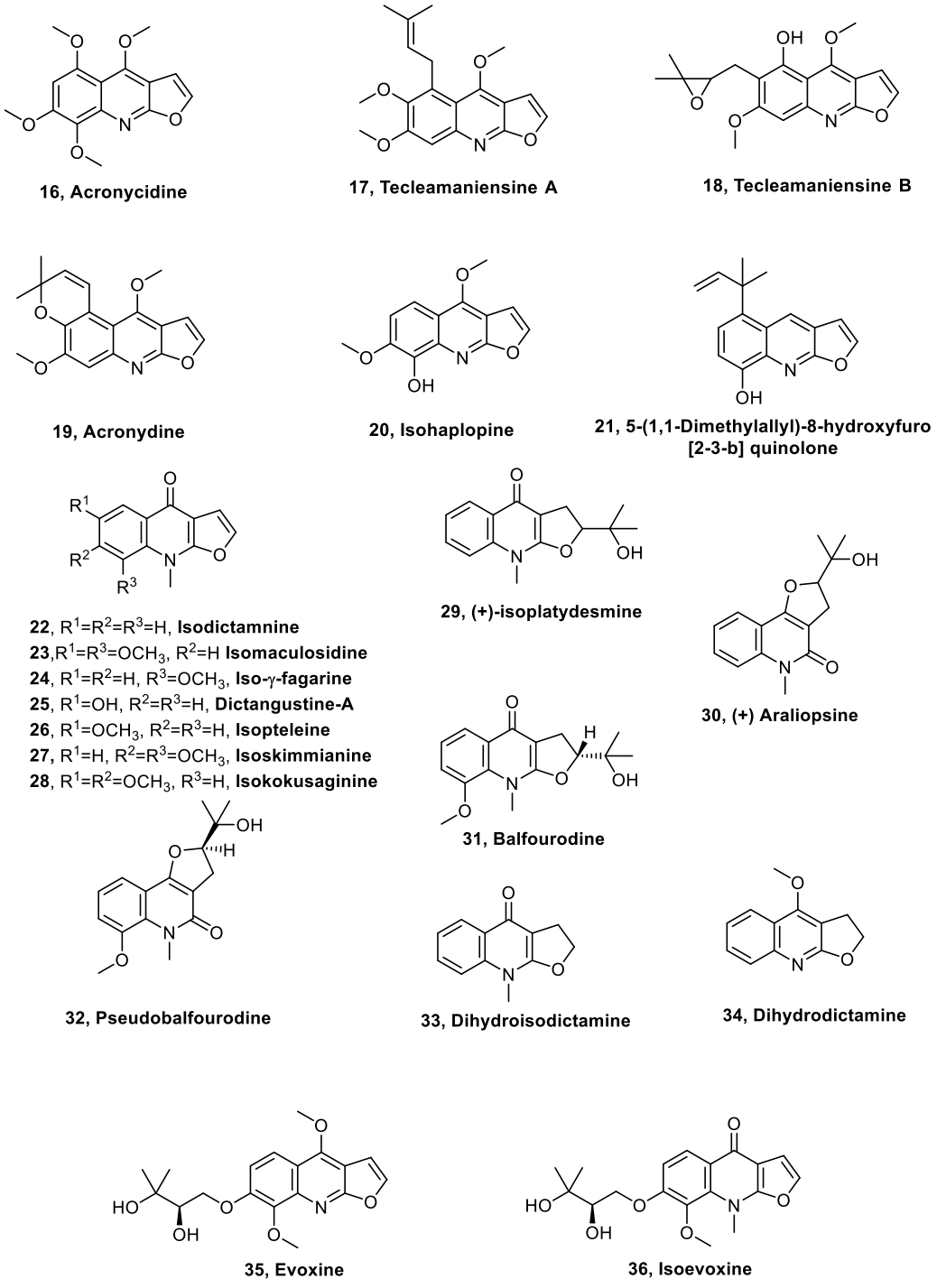


Figure 1. Structures of furoquinoline alkaloids isolated from Rutaceae.

The ability of γ-fagarine (**3**) to induce SCEs in human lymphocytes was demonstrated.[23] Further, Nganou *et. al.* in 2019 reported the ability of maculine to be helpful in the fight against multi-drug resistant (MDR) cancer cells.[24]

The present review highlights the sources, ways of extraction, and the methods of synthesis as well as the biological efficacy of maculine (**8**) as one of Rutaceae family alkaloids.

2.1. Botanical Sources

Maculine is a furoquinoline alkaloid widely spread in the bark of several Flindersia; a genus of 17 species of trees in the family Rutaceae. They grow naturally in the Moluccas, New Guinea, Australia, and New Caledonia.[25–27] Also, maculine was isolated from the root bark of *Araliopsis soyauxii* (family Rutaceae).[13] Maculine was identified in the leaves and the fruits of *Teclea nobilis,* a tropical African medicinal plant (Rutaceae).[14] It was separated from the stem bark of *Araloiopsis tabouensis* Aubrev and Pellegr (Rutaceae); the large tropical west African tree whose bark used in the folk medicine for the treatment of gonorrhea.[17] Maculine is abundant in *Esenbeckia,* which is a genus of ca 30 species, native in tropical America.[28] Species of this genus are known as a source of a variety of typical rutaceous secondary metabolites.[29,30] Thus, maculine was isolated from *E. almawillia* and *E. grandiflora*[9] and the leaves of *Esenbeckia litoralis* collected from Temascal, Oaxaca, Mexico.[31]

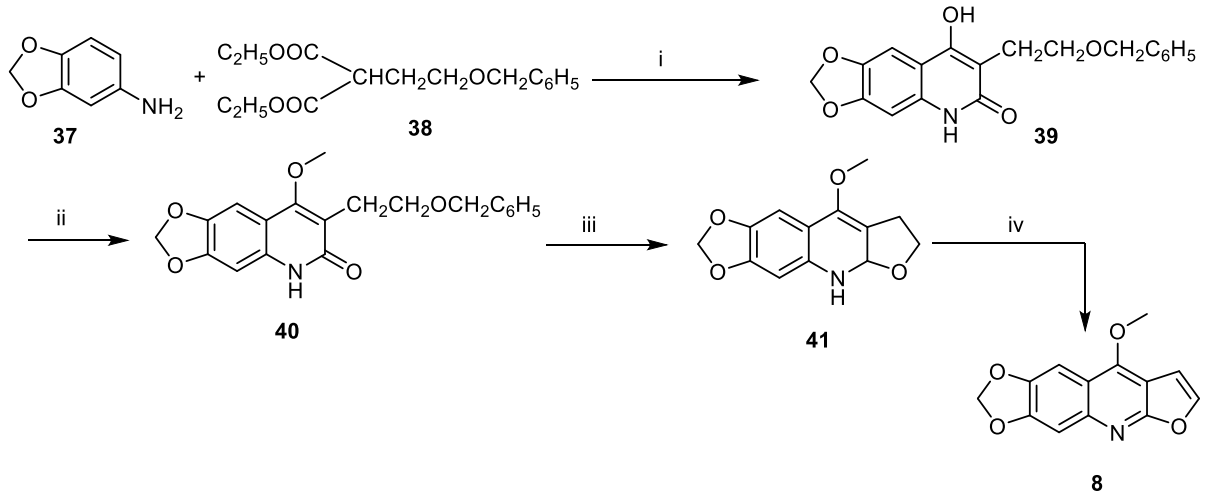
The phytochemical investigation of the hexane extract from the roots of *Esenbeckia grandiflora* subsp. *grandiflora var. grandiflora* (Rutaceae), native to tropical America allowed the identification of maculine.[32] Furthermore, the methanol extract of the roots of *Esenbeckia almawillia* (Rutaceae) was a source of maculine.[33] *Esenbeckia leiocarpa* (Rutaceae), popularly known as *guarantã, goiabeira*, a native tree of Brazil, afforded maculine.[16] Another plant of family Rutaceae, *Oricia suaveolens* expressed maculine in the stems and leaves extract. This plant could be found in the Democratic Republic of the Congo, Ivory Coast, Ghana, Guinea, Nigeria, and Sierra Leone.[34] The widespread nature of maculine in Rutaceae was further confirmed by investigation of *Zanthoxylum buesgenii* and *Teclea afzelii* which represented another source of this alkaloid.[35] This last is a tropical African plant, distributed from Sierra Leone to Cameroon and used in Cameroonian folk medicine in the treatment of wound infections, abdominal pains, cough, fever and asthma.[15] Recently maculine was isolated from the methanol extract of the stem bark of *Araliopsis soyauxii* (Rutaceae).[24]

Table 1. The various sources of masculine and its extraction from different parts of Rutaceae plants

Genus	Species	Part of plant	Solvent of extraction	Ref
Teclea	*nobilis*	Leaves and fruits	Ethanol	14
Teclea	*nobilis*	Roots	Dichloromethane: methanol (1:1) and methanol	35
Esenbeckia	*leiocarpa*	Stems	Ethanol	30
Esenbeckia	*almawillia*	Roots	Methanol	31
Teclea	*afzelii*	Stem bark	Methanol	15, 19
Flindersia	*maculosa*	Stem bark	Methanol	36, 37
Araliopsis	*soyauxii*	Root and stem bark	Petroleum ether and chloroform	19
Araliopsis	*soyauxii*	stem barks and leaves	Methanol	34
Zanthoxylum	*buesgenii*	Aerial parts	Dichloromethane: Methanol (1:1)	33
Araliopsis	*tabouensis*	Root and steam bark	Hexane and chloroform	17
Raulinoa	*echinata*	Stems and leaves	Hexane and MeOH	38
Esenbeckia	*almawillia*	Trunk bark	n-Hexane and EtOH	9
Esenbeckia	*grandiflora*	Roots	Ethanol, then n-hexane, $CHCl_3$ and EtOAc	9
Esenbeckia	*litoralis*	Leaves	Ethyl acetate	29
Vepris	*punctata*	Wood	CH_2Cl_2/MeOH	39
Oricia	*suaveolens*	Stems and leaves	Methanol	32

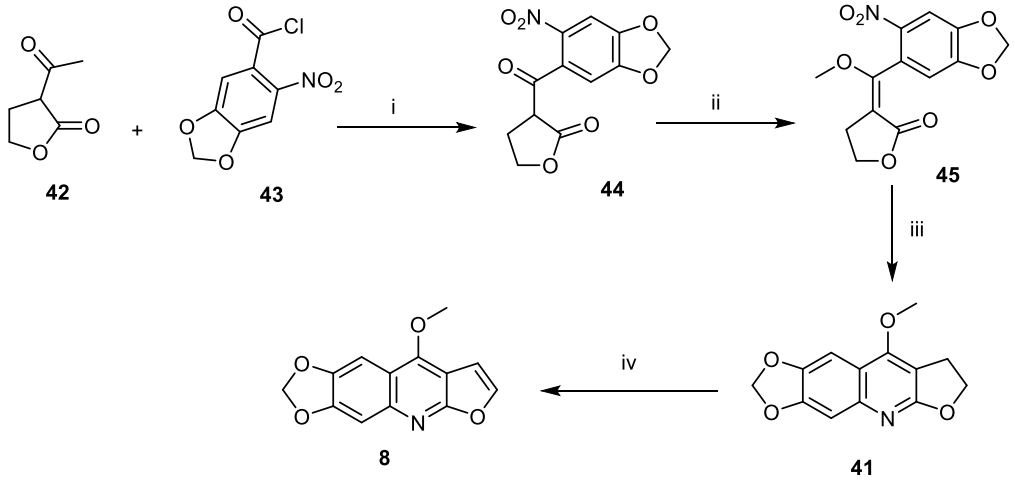
3. Organic Synthesis

Maculine has been synthesized in three different pathways. Firstly, it was prepared by condensation of 3,4-methylenedioxyaniline (**37**) with diethyl (2-benzyloxyethyl)malonate (**38**) to afford 3-(2-benzyloxyethyl)-4-hydroxy-6,7-methylenedioxycarbostyril (**39**). Compound **39**, in turn, was methylated by diazomethane to provide the corresponding 4-methoxy compound **40**. Cyclization of **40** by the action of polyphosphoric acid yielded 4-methoxy-6,7-methylenedioxy-2,3-dihydrofuro[2,3-*b*]quinoline (**41**) which produced the final product **8** (mp 195-196 °C) under dehydrogenation with *N*-bromosuccinimide (Scheme 1).[38]



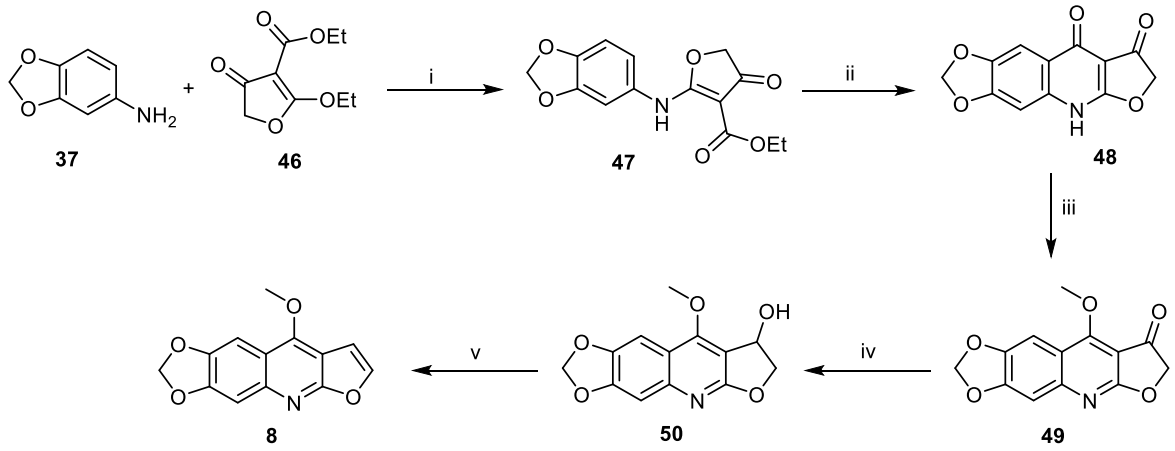
Scheme 1. Synthesis of Ohta and Mori.[38] *Reagents and conditions*: (i) EtOH 2mol, diphenyl ether, heat, 30min, aq NaOH 5%, yield 45%; (ii) diazomethane, Et_2O, 0-5°C overnight, aq KOH 5%, yield 77%; (iii) polyphosphoric acid, heat, 1h, yield 31%; (iv) *N*-bromosuccinimide, AcOH, AcONa, CCl_4, heat, 4h, aq NaOH 2%, yield 51%.

Zimmer and Walter [43] reported a new pathway for synthesis of maculine *via* the utilization of certain substituted *α*-benzylidene-γ-butyrolactones. Condensation of acetyl-butyrolactone (**42**) with 2-nitro-4,5-methylenedioxybenzoyl chloride (**43**) gave the corresponding 3-(6-nitro[1,3]benzodioxole-5-carbonyl)-dihydrofuran-2(3*H*)-one (**44**). The reaction of **44** with diazomethane produced (*E*)-3-[methoxy-3-(6-nitro[1,3]benzodioxol-5-yl)methylene]dihydrofuran-2(3*H*)-one (**45**). Upon reduction of NO_2 group of **45** using Pd/C in presence of methanolic HCl led to the formation of dihydromaculine **41**. Aromatization of **41** upon refluxing and irradiating using UV-light in presence of an equivalent amount of *N*-bromosuccinimide in CCl_4, followed by refluxing the residue with collidine gave **8**.[43] (Scheme 2). Kuwayama[44] has used a similar route using magnesium, CCl_4, ethanol instead of sodium in the first step, and sodium methoxide for the aromtization of **41** instead of collidine.



Scheme 2. Synthesis of Zimmer and Walter.[43] *Reagents and conditions*: (i) Na, MeOH yield 36%; (ii) diazomethane, C_6H_6, 0-5°C, 5 days yield 91%; (iii) Pd/C, methanolic-HCl yield 72%; (iv) a: NBS, CCl_4, reflux, 30-40min, UV-light, b: collidine, reflux.

In the last reported pathway, Yazima and Munakata demonstrated the synthesis of maculine starting with ethyl 2-([1,3]benzodioxol-5-ylamino)-4-oxo-4,5-dihydrofuran-3-carboxylate (**47**). Thermal ring closure of the ester **47** under fusion led to the formation of [1,3]dioxolo[4,5-*g*]furo[2,3-*b*]quinoline-8,9(5*H*,7*H*)-dione (**48**). Methylation of **48** by reaction with diazomethane in dioxane yielded **49**. Reduction of the furanone **49** using sodium borohydride gave the corresponding furanol **50**. Dehydration of **50** furnished masculine (**8)** in 40% yield.[45] (Scheme 3)



Scheme 3: Synthesis of Yazima and Munakata. *Reagents and conditions*: (i) a: compound **37**, TEA, r.t., dry THF, stirring, 40min, b: compound **46**, Na, dry DHF, 0°C, α-chloropropionic acid, stirring, 40min, c: mixture of a and b with a, reflux, 20min, yield 10%; (ii) heat at 250°C, vigorous stirring, 20min, inert gas, yield 91%; (iii) diazomethane, dioxane, yield 40%; (iv) dry methanol, dry THF, sodium borohydride, stirring, 0°C, yield 31%; (v) dry dioxane, fused potassium bisulfate, refluxed, 45min, yield 40%.

4. Biological Activity

Although maculine showed varieties of biological activities that ranged from antimicrobial to antitumor, it has not yet been reported to possess a significant activity toward some particular targets. It revealed a phototoxic activity to certain yeasts (*Saccharomyces cerevisiae*), fungi (*Candida albicans*), and bacteria (*Streptococcus faecalis*) in long wave UV light.[20] This antimicrobial activity was further investigated by the disk diffusion method against *Staphylococcus aureus* in which the inhibition zone was moderate (9 mm) compared to the standard Ceftriaxone (20 mm).[36] Certain strains of bacteria and fungi were subjected to additional antimicrobial assays of maculine. The recorded antimicrobial activity in this assay was 87.5% against *Escherichia coli, Pseudomonas aeruginosa, Staphylococcus aureus, Bacillus subtilis, Candida albicans, Candida gabrata, Salmonella typhimurum* and *Microsporum audorium.*[46]

The maximum efficacy as an antibacterial agent was observed against *Bacillus subtilis.* It recorded minimal microbial concentration MMC of 2.44 µg/ml (two-fold) lower than the reference gentamicin (MMC 4.22 µg/ml). Besides, it showed moderate activity against mycobacteria *M. smegmatis* with a minimal inhibition concentration MIC of 156.25 µg/ml compared to Ciprofloxacin.[46] The antiparasitic characteristic of maculine was studied against trypomastigote forms of *Trypanosoma cruzi* and malaria and it was moderate for both parasites.[19,47]

Additionally, this furoquinoline alkaloid revealed a photo-mutagenic effect against a mutant strain of *Chlamydomonas reinhardtii* using a dose of 40 µg/ml with exposure of the cells to irradiation with UV-A.[10,48] Its photosensitizer activity could be attributed to the planar structure, and so its capability of intercalating into DNA.[48] Maculine displayed selective and moderate cytotoxic activity, and the data highlighted the possibility of using maculine to fight drug-sensitive and resistant cancers.[24] It was tested on A2780 human ovarian cancer cell and the cytotoxicity was moderate of IC_{50} value = 4.2 µg/ml.[40] Recently maculine was screened *in vitro* for its effect on the viability of two different human cancer cell lines, namely prostate PC-3 adenocarcinoma cells and colorectal HT-29 adenocarcinoma cells. The results revealed that maculine showed some antiproliferative effect, but exclusively on HT-29 cells at 100 µM.[42]

5. Conclusions

Maculine is a furoquinoline alkaloid which is abundant in the Rutaceae family. Many species subclassified under this family have introduced a resource of this alkaloid. It could be noticed the lack of interest in the searching of analogues of masculine or even to develop more alternative synthetic procedures for its fabrication. We tried in this mini-review to draw attention toward this nitrogenous compound which however has not shown a breakthrough regarding the biological activity it could act as an aspect for drug discovery *via* structure optimization or as an inspiring scaffold.

Acknowledgements

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