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# Chemical constituents of *Morina* genus: a comprehensive review

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## Abstract

*Morina*, a genus (family: Caprifoliaceae) of perennial herbs revered for their aromatic character and medicinal value is widely distributed in nature. Of the six accepted species of *Morina*, five species viz: *M. chinensis*, *M. kokonorica*, *M. longifolia*, *M. nepalensis* var. *alba* and *M. persica* have been the subject of numerous chemical investigations which has led to the characterization of a large number of chemical constituents in their different parts. The secondary metabolites reported in these species for the period upto 2013 are reviewed and compiled in this paper. Altogether one hundred ninety seven chemical constituents including one hundred eight volatile compounds, and eighty nine non-volatile compounds in the roots, leaves and whole plant of these species are listed together with their sources and references. These have been categorized into phenylpropanoids, sterol, iridoids, terpenes, lignans, neolignans, phenolics, and miscellaneous compounds. Biological activities associated with these compounds have also been given.

Keywords: Morina, Caprifoliaceae, Phytochemicals.

# 1. Introduction

Morina (family: Caprifoliaceae) is a genus of angiosperms. Its name was derived from the Louis-Pierre Morin (1635-1715), a French physician and botanist <sup>[1]</sup>. Within Caprifoliaceae, besides genus Morina, two other genera Acanthocalyx (A. alba, A. albus, A. delavayi, A. nepalensis), and Cryptothladia (C. chinensis, C. chlorantha, C. kokonorica, C. ludlowii, C. parviflora, C. polyphylla) extending from southeastern Europe and Israel to the Himalayas of Nepal, Bhutan and China, and further east and north in the Oinghai-Tibetan Plateau are also recognized <sup>[2-4]</sup>. These plants grow in different habitats including rock ledges, alpine meadows, dry slopes, the margins of pine forests, and even swamps at high altitude sometimes more than 4200 m<sup>[4]</sup>. According to Tropicos<sup>®</sup>, The Plant List for the genus Morina includes thirteen species, of which six species namely Morina chinensis Diels ex Grüning, Pax & K. Hoffm., M. chlorantha Diels, M. kokonorica K.S. Hao, M. longifolia Wall, M. lorifolia C.Y. Cheng & H.B. Chen, M. nepalensis D. Don are accepted species, and seven are synonyms of the accepted infraspecific names. Morina chinensis, M. chlorantha, M. kokonorica, M. nepalensis var. alba, M. nepalensis var. delavayi, and M. nepalensis var. nepalensis are reported to occur in mountainous regions at the altitude between 2800 and 4900 m in the northwest and southwest of China <sup>[5]</sup>. M. longifolia is distributed in the temperate and alpine region of the Himalayas from Kashmir to Bhutan at an altitude of 2400-4200 m<sup>[6]</sup>.

Some species of the genus *Morina* such as *Morina chinensis*, *M. kokonorica*, *M. nepalensis* var. *alba*, and *M. nepalensis* var. delavayi have been used as Chinese traditional medicines for the treatment of cerebral apoplexy, arthralgia, lumbago, megrim, tumors <sup>[7]</sup>. Use of *M. longifolia* in traditional systems of medicines is also reported. The stem, leaves and flowers owing to their sweet and astringent taste with a heating potency are used in Tibetan medicine <sup>[6]</sup>. The roots and the flowers are used as poultice on boils and wounds and for unconsciousness, respectively, in Indian traditional medicine <sup>[8]</sup>. The use of the plant as veterinary medicine in treatment of maggot wounds is also documented <sup>[9]</sup>.

# 2. Chemistry of Morina genus

The chemistry of Morina genus has been examined. Chemical investigation of five Morina species viz: M. chinensis, M. kokonorica, M. longifolia, M. nepalensis var. alba and M. persica (this species in The Plant List of Tropicos® is an unresolved name and is not established either as an accepted name or as a synonym), led to the characterization of a large number of chemical constituents in their different parts. During the course of phytochemical examination of *M. longifolia* aiming to isolate and characterize its bioactive compounds, we conducted the review of literature with special reference to the chemistry of different Morina species examined so far. A review on chemical constituents of M. chinensis, M. kokonorica, M. longifolia, and M. nepalensis is previously reported <sup>[10]</sup> in which traditional medicinal uses of M. chinensis and M. longifolia along with the antimicrobial activities of *M. longifolia* essential oil and its different extracts are given. The lack of a comprehensive review on the chemistry of Morina genus prompted us to compile a review on the secondary metabolites characterized in different Morina species. The present review, covering the literature up to 2013 including our work on phytochemistry of *M. longifolia*<sup>[11]</sup>, gives an account of plant part wise various compounds characterized in different Morina species. Emphasis has also been given on the biological activities associated with these compounds.

The review of literature reveals presence of altogether one hundred ninety seven chemical constituents including one hundred eight volatile compounds, and eighty nine non-volatile compounds (Table 1) in different parts of five Morina species. These have been categorized into phenylpropanoids, sterol, iridoids, terpenes, lignans, neolignans, phenolics and miscellaneous compounds. The terpenoids are widely distributed in the genus and found in all the species except *M. chinensis*. Due to strong aromatic character of the aerial parts of Morina plants, their chemistry has been investigated. Monoterpenoids and sesquiterpenoids constituting the essential oils of M. longifolia, and M. persica have been characterized using GC-MS. The essential oil obtained from the aerial parts of M. longifolia, occurring in Gopeshwar Forest Division, Uttarakhand contained six monoterpenoids (β-myrcene, geraniol formate, limonene, Z-citral, dihydrocarveol, p-menth-1en-3,8-diol), and six sesquiterpenoids ( $\alpha$ -gurjunene, germacrene-D, 2,3-dihydrofarnesol, aromadendrene. β-cadinene and constituent of the oil<sup>[12]</sup>. Six monoterpenoids (myrcene, limonene, cis-p-menth-2-en-1-ol, ipsdienol, trans-p-menth-2-en-1-ol, transpiperitol), and seventeen sesquiterpenoids (β-bourbonene, βelemene, β-ylangene, β-caryophyllene, β-copaene, β-humulene, γmuurolene, germacrene-D,  $\alpha$ -*E*,*E*-farnesene, bicyclogermacrene,  $\alpha$ - $\gamma$ - and  $\delta$ - cadinene, -germacrene-D-4-ol, 1-epi-cubinol, epi- $\alpha$ muurolol,  $\alpha$ -cadinol) were characterized in the essential oil isolated from the leaves of M. longifolia, grown in Chakrata Forest Division, Uttarakhand. Germacrene-D (60) was the principal constituent of the oil [11]. Antioxidant and antimicrobial activities of these essential oils were determined and attributed to their monoand Sesquiterpenoids <sup>[12, 13]</sup>. The volatile oil isolated from the aerial part of *M. longifolia* found in Milam glacier of Kumaun Himalayas reported to consist of thirty monoterphoids, (tricyclene,  $\alpha$ -thujene,  $\alpha$ - and  $\beta$ -pinene, camphene, sabinene, myrcene,  $\alpha$ - and β- phellandrene, α-terpinene, p-cymene, 1,8-cineol, (Z)- and (E)- βocimene, cis- and trans-sabinene hydrate, terpinolene, linalool, trans-thujone, cis- and trans-p-menth-2-en-1-ol, chrysanthenone, borneol, terpinen-4-ol, α-terpineol, verbenone, citronellol, bornyl acetate, trans-sabinyl acetate, citronellyl acetate), thirty five sesquiterpenoids ( $\delta$ -elemene,  $\alpha$ - and  $\beta$ -cubebene,  $\beta$ -bourbonene,  $\alpha$ -, β- and γ-gurjunene, β-caryophyllene, α-humulene, α- and γmuurolene, germacrene-D, cis-\beta-guaine, bicyclogermacrene, germacrene-A, cubebol, δ-cadinene, germacrene-B, germacrene-D-4-ol, spathulenol, carvophyllene oxide, humulene epoxide-II, 10-epi- $\gamma$ - eudesmol,  $\beta$ - and  $\gamma$ -eudesmol, epi- $\alpha$ -cadinol,  $\alpha$ -cadinol, bulsenol, (E)-citronellyl tiglate,  $\alpha$ - and  $\beta$ -bisabolol, (Z,E) and (E,E)-farnesol, curcumenol, oplopanone), and two diterpenes (pimaradiene, sandaracopimara-8(14),15-diene) with germacrene-D (60) as the chief constituent<sup>[14]</sup>. *M. persica* flower essential oil contained three monoterpenoids (citronellol, geranyl acetone, geranyl linalool), and thirteen sesquiterpenoids ( $\alpha$ -copaene,  $\beta$ bourbonene, germacrene-D, bicyclogermacrene,  $\alpha$ -farnesene,  $\delta$ cadinene, (E)-nerolidol, hexahydrofarnesylacetone, T-muurolol,  $\alpha$ cadinol, (2E,6E)-farnesyl acetate, (2E,6E)-farnesol, (2E,6E)farnesyl butyrate with (2E, 6E)-farnesol (89) as the main constituent<sup>[15]</sup>.

Twenty two triterpenoids including six triterpene acids with ursane (39,46,47,51,52) and oleanane (55) skeleton, and sixteen triterpenoid saponins represented by taraxastane (42,43), ursane (68-74) and oleanane (75-81) groups have been isolated from the leaves of *M. longifolia* and the whole plant of *M. kokonorica* and *M. nepalensis*. Triterpenoids with pentacyclic skeleton of ursane and oleanane have been found to possess anticancer, anti-HIV and anti-inflammatory activities <sup>[16, 17]</sup>.

Next class of constituents is represented by twenty three phenylpropanoids from *M. chinensis* and *M. nepalensis*. These include seven phenyl propanol esters (1-6,10), one phenyl propene (7), two phenyl propanols (8,12), two phenyl propanol ethers (9,22), one phenyl propenal (23), and nine phenyl propanol ester lipids (13-21) in the roots of M. chinensis, and one phenylpropanoid glycoside (83) accumulated in M. nepalensis plant. The phenylpropanoids whole synthesized from phenylalanine are a diverse family of organic compounds, consisting of C<sub>6</sub> aromatic phenyl group and C<sub>3</sub> propene tail of cinnamic acid. Phenylpropanoids have been found to be associated with biological activities including antifungal, antibacterial, nematocidal and molluscicidal activities [18].

Presence of fifteen phenolic compounds has been recorded in *M. kokonorica*, *M. nepalensis*, and *M. longifolia* including eight flavonoid glycosides, three phenolic acids and four phenolic acid esters. There were seven flavonol glycosides (**38** in *M. kokonorica* whole plant, (**61-66**), one flavone glycoside (**67**), two phenolic acids (**57**, **84**), and four caffeoylquinic acids (**85-88**) characterized in *M. nepalensis* whole plant while two phenolic acids (**57**, **58**) were found in the leaves of *M. longifolia*. Caffeoylquinic acids are the ester of caffeic acid and quinic acid. 3-*O*-caffeoyl quinic acid is an important intermediate in lignin biosynthesis and is also an antioxidant <sup>[19]</sup>. Protocatechuic acid (**84**) is a major metabolite of antioxidant polyphenols in green tea. It is antioxidant, anti-inflammatory and anticancer <sup>[20]</sup>.

Lignans and neolignans are very important class of natural products and have attracted much interest both on account of their widespread occurrence in nature as well as several biological activities including contraceptive, antitumor, antiviral and cytotoxic activities <sup>[21-25]</sup>. Lignans constitute a family of optically active plant products and consist of two C6-C3 units linked at βcarbons of the side chain <sup>[26]</sup>. The lignans such as pinoresinol (36) and lariciresinol (37) have been isolated from the roots of M. chinensis while (+)-pinoresinol (48) and (-)-lariciresinol (49) have been characterized in the whole plant of *M. kokonorica*. The term neolignans was introduced by Gottlieb [27] to designate compounds in which the two C<sub>6</sub>-C<sub>3</sub> units are not inked by  $\beta$ - $\beta'$  bond. Fifteen neolignans have been characterized in the Morina species. Su et al., 1999<sup>[25]</sup> have reported isolation of twelve neolignans (24-35) in the roots of *M. chinensis*. Morinol A (24) and morinol B (25) bear a tetrahydropyran ring with a new carbon skeleton. In morinols C-L (26-35), the two units C<sub>6</sub>-C<sub>3</sub> were linked from C-8 ( $\beta$ ) to C-9 ( $\gamma$ ) by a C-C bond directly. Morinols C-H (26-31) were three pairs of threo and erythro isomers. The induction of cytokines in human peripheral blood mononuclear cells by various species of mycoplasmas and the interleukin  $-1\alpha$  (IL- $1\alpha$ ) and  $1\beta$  ((IL- $1\beta$ ) production in peripheral whole blood from patients with urological cancer have been reported <sup>[28]</sup>. Morinol A and morinol B were examined for their inhibitory effects on cytokinine production wherein morinol B had stronger activity than morinol A <sup>[25]</sup>. Four neolignans (30, 44, 45, 50) were characterized in the M. kokonorica whole plant.

Steroids in *Morina* genus are represented by  $\beta$ -Sitosterol (41) which has been identified in *M. kokonorica* whole plant and *M.* 

*longifolia* leaves. Iridoids are of biogenetic and chemotaxonomic importance and have displayed various biological activities <sup>[29-30]</sup>. Iridoids have been shown to have complex stereochemistry as a large number of enantiomeric iridoids have been identified <sup>[31-35]</sup>. One iridoid glycoside has been isolated from water soluble fraction of ethanol extract of *M. nepalensis* whole plant and was identified as 7-deoxyloganic acid (**82**). 7-Deoxyloganic acid and its derivatives are important precursors of some other kinds of iridoids. In biosynthetic experiments, incorporation of 7-deoxyloganic acid into the trans-fused iridoid glycosides (5 $\alpha$ *H*)-6-epi-dihydrocornin and 10-hydroxyl-(5 $\alpha$ *H*)-6-epi-dihydrocornin in *Penstemon secundiflorus* led to the hydroxylation of deoxyloganic acid to form loganic acid with retention of the 7 $\alpha$ -hydrogen followed by ring cleavage to give secologanic acid <sup>[32, 36]</sup>.

Beside the above mentioned categories of compounds, five compounds isolated from *Morina* species are grouped under miscellaneous type. These include long chain organic acid (40) from *M. kokonorica* whole plant, long chain aliphatic ketone (53), substituted long chain aliphatic alcohol (54), and aromatic acid glycoside (56) from the leaves of *M. longifolia*, and substituted aromatic aldehyde (11) from *M. chinensis* roots. Besides, four aliphatic hydrocarbons (pentadecane, octadecane, pentacosane and heptacosane), four aliphatic aldehydes (n-decanal, heptanal, dodecanal, n-tetradecanal), two aliphatic alcohols (1-decanol and 2-octanol), two aliphatic ketones (2-octanone and 6-methyl-5-heptane-2-one), aromatic aldehyde (benzaldehyde), and aliphatic ester ((*E*)-2-hexenyl benzoate) have also been characterized in *M. longifolia* essential oils <sup>[11-12, 14]</sup>.

**Table 1:** Chemical constituents characterized in *Morina* genus.

S. No.	Morina species	Parts	Chemical constituent (Constituent structure)	References
	<i>M. chinensis</i> Diels ex Grüning, Pax & K. Hoffm.	Roots	Morinin A (1) Morinin B (2)	
			Morinin C ( <b>3</b> )	[37]
			Morinin D (4)	
			Morinin E (5)	
			Morinin F (6)	
			Morinin G (7)	
			4-O-Methylcinnamyl alcohol (8)	
			4-O-Methylcinnamyl methyl ether (9)	
			4-O-Methylcinnamyl acetate (10)	
			<i>p</i> -Methoxybenzaldehyde (11)	
			4- <i>O</i> -Methyl-( <i>E</i> )-coniferyl alcohol ( <b>12</b> )	
			Morinin H ( <b>13</b> )	
			Morinin I (14)	
1			Morinin J (15)	[38]
1.			Morinin K (16)	
			Morinin L ( <b>17</b> )	
			Morinin M (18)	
			Morinin N ( <b>19</b> )	[39]
			Morinin O (20)	
			Morinin P (21)	
			3,4-Dimethoxycinnamylalcoholmethyl ether (22)	
			<i>p</i> -Methoxycinnamaldehyde (23)	
			Morinol A ( <b>24</b> )	
			Morinol B (25)	
			Morinol C (26)	
			Morinol D (27)	[25]
			Morinol E ( <b>28</b> )	
			Morinol F (29)	

			Morinol G ( <b>30</b> ) Morinol H ( <b>31</b> ) Morinol I ( <b>32</b> ) Morinol J ( <b>33</b> ) Morinol K ( <b>34</b> ) Morinol L ( <b>35</b> ) Pinoresinol ( <b>36</b> ) Lariciresinol ( <b>37</b> )	
			Rutin (38) Ursolic acid (39) Melissic acid (40) $\beta$ -Sitosterol (41) ((+11+)) (1/2-0) Acted a Lagradian provide a subsequence of the set of	[40]
2.	<i>M. kokonorica</i> K.S. Hao	Whole plants	$(6a, 11a)-6-[(2-O-Acety]-a-L-arabinopyranosy1)oxy] -3-oxotaraxast-20-ene-11,28-diyl diacetate (42)(6a, 11a)-6-[(2-O-Acetyl-\beta-D-xylopyranosyl)oxy] -3-oxotaraxast-20-ene-11,28-diyl diacetate (43)(1R,2R,4E)-1,5-Bis(3,4-dimethoxyphenyl)-2-(methoxymethyl)pent-4-en-1-ol (44)1,1'-[(1E,4R,5R)-5-Methoxy-4-(methoxymethyl)pent-1-ene-1,5-diyl] bis(3,4-dimethoxybenzene) (45)3\beta-Hydroxyurs-12-en-28-al(=ursolaldehyde) (46)3\beta-Hydroxyurs-11-en-8,13\beta-olide (47)Morinol G (30)(+)-Pinoresinol (48)(-)-Lariciresinol (49)Balanophonin (50)$	[41]
			Morinoursolic acids A ( <b>51</b> ) Morinoursolic acids B ( <b>52</b> ) <i>n</i> -Triacont-3-one ( <b>53</b> ) 8-Methylditriacont-7-ol ( <b>54</b> ) β-Sitosterol ( <b>41</b> )	[42]
3.	M. longifolia Wall.	Leaves	Oleonolic acid (55) 2,6-Dihydroxy-5-methoxy-(3-C-glucopyranosyl) benzoic acid (56) $\beta$ -Sitosterol (41) E-Caffeic acid (57) p-Hydroxybenzoic acid (58)	[43]
			Essential oil ( <b>59, 60</b> )	[11-12, 14]
			Quercetin 3- <i>O</i> -[2''- <i>O</i> -( <i>E</i> )-caffeoyl]-α-L-arabinopyranosyl-(1→6)-β-D- galactopyranoside ( <b>61</b> ) Quercetin 3- <i>O</i> -[2'''- <i>O</i> -( <i>E</i> )-caffeoyl]-α-L-arabinopyranosyl-(1→6)-β-D- galactopyranoside (Monepalin A) ( <b>62</b> ) Quercetin 3- <i>O</i> -[2'''- <i>O</i> -( <i>E</i> )-caffeoyl]-α-L-arabinopyranosyl-(1→6)-β-D- glucopyranoside (Monepalin B) ( <b>63</b> ) Quercetin 3- <i>O</i> -α-L-arabinopyranosyl-(1→6)-β-D-galactopyranoside (Rumarin) ( <b>64</b> ) Quercetin 3- <i>O</i> -β-D-galactopyranoside ( <b>65</b> ) Quercetin 3- <i>O</i> -β-D-glucopyranoside ( <b>66</b> ) Apigenin 4'- <i>O</i> -β-D-glucopyranoside ( <b>67</b> )	[45]
4.	<i>M. nepalensis</i> var. <i>alba</i> Hand-Mazz.	Whole plants	(Monepaloside A) (68) (Monepaloside B) (69) $3-O-\alpha$ -L-Arabinopyranosyl-( $1\rightarrow 3$ )-[ $\alpha$ -L-rhamnopyranosyl-( $1\rightarrow 2$ )]- $\alpha$ -L- arabinopyranosylpomolic acid $28-O-\beta$ -D-glucopyranosyl-( $1\rightarrow 6$ )- $\beta$ -D- glucopyranoside (Monepaloside C) (70) $3-O-\alpha$ -L-Arabinopyranosyl-( $1\rightarrow 3$ )-[ $\alpha$ -L-rhamnopyranosyl-( $1\rightarrow 2$ )]- $\beta$ -D- xylopyranosyl- pomolic acid $28-O-\beta$ -D-glucopyranosyl-( $1\rightarrow 6$ )- $\beta$ -D-glucopyranoside (Monepaloside D) (71) $3-O-\alpha$ -L-Arabinopyranosyl-( $1\rightarrow 3$ )-[ $-\beta$ -D-glucopyranosy-( $1\rightarrow 2$ )]- $\alpha$ -L- arabinopyranosyl- pomolic acid $28-O-\beta$ -D-glucopyranosyl-( $1\rightarrow 6$ )- $\beta$ -D-glucopyranoside (Monepaloside E) (72) $3-O-\beta$ -D-Xylopyranosylpomolic acid $28-O-\beta$ -D-glucopyranoside (Monepaloside F) (73) Mazusaponin II (74)	[46]

			<ul> <li>3-<i>O</i>-α-L-Arabinopyranosyl (1→3)-α-L-arabinopyranosyl oleanolic acid 28-<i>O</i>-β-D-glucopyranosyl-(1→6)-β-D-glucopyranoside (Monepaloside G) (<b>75</b>)</li> <li>3-<i>O</i>-α-L-Arabinopyranosyl-(1→3)-β-D-xylopyranosyl oleanolic acid 28-<i>O</i>-β-D-glucopyranosyl oleanolic acid 28-<i>O</i>-β-D-glucopyranosyl oleanolic acid 28-<i>O</i>-β-D-glucopyranosyl-(1→3)-β-D-glucopyranosyl-(1→2)]-α-L-arabinopyranosyl oleanolic acid 28-<i>O</i>-β-D-glucopyranosyl-(1→6)-β-D-glucopyranoside (Monepaloside I) (<b>77</b>)</li> <li>3-<i>O</i>-β-D-Glucopyranosyl-(1→4)-β-D-glucopyranosyl-(1→3)-α-L-arabinopyranosyl oleanolic acid 28-<i>O</i>-β-D-glucopyranosyl-(1→3)-α-L-arabinopyranosyl oleanolic acid 28-<i>O</i>-β-D-glucopyranosyl-(1→6)-β-D-glucopyranosyl oleanolic acid 28-<i>O</i>-β-D-glucopyranosyl oleanolic acid 28-<i>O</i>-β-D-glucopyranosyl oleanolic acid 28-<i>O</i>-β-D-glucopyranosyl oleanolic acid 28-<i>O</i>-β-D-glucop</li></ul>	[47]
			3-O-α-L-Arabinopyranosyl-(1→3)-β-D-xylopyranosyl- staresinolic acid (Monepaloside K) ( <b>79</b> ) 3-O-β-D-Arabinopyranosyl-(1→3)-α-D-xylopyranosyl staresinolic acid 28-O-β- D-glucopyranosyl-(1→6)-β-D-glucopyranoside (Monepaloside L) ( <b>80</b> ) Mazusaponin I ( <b>81</b> )	[48-49]
			7-Deoxyloganic acid (82) Citrusin C (83) 3,4-Dihydroxyl benzoic acid (84) ( <i>E</i> )-Caffeic acid (57)	[30]
			3-O-Caffeoylquimic acid ( <b>85</b> ) 3,5-di-O-Caffeoylquimic acid ( <b>86</b> ) 4,5-di-O-Caffeoylquimic acid ( <b>87</b> ) 3,4-di-O-Caffeoylquimic acid ( <b>88</b> )	[50]
5.	M. persica Linn.	Leaves	Essential oil (89)	[15]



(1) R<sub>1</sub>=R<sub>2</sub>=R<sub>3</sub>=H
 (2) R<sub>1</sub>=OCH<sub>3</sub>; R<sub>2</sub>=R<sub>3</sub>=H

(3) R<sub>1</sub>=OCH<sub>3</sub>; R<sub>2</sub>=OH; R<sub>3</sub>=H

(4) R<sub>1</sub>=R<sub>3</sub>=H; R<sub>2</sub>=OAng

(5) R1=R2=H; R3=OAng

(6) R<sub>1</sub>=R<sub>3</sub>=H; R<sub>2</sub>=OSen











~ 5 ~

Sen=











(19)



(20)



(21)









(34)



~ 8 ~





































(74) R<sub>1</sub>=H; R<sub>2</sub>=H





CH₃ HO -0 (71) R<sub>1</sub>= ΗÓ OH





(73) R<sub>1</sub>=H; R<sub>2</sub>=H; R<sub>3</sub>=H



HO

 $R_2 =$ 











# 3. Acknowledgement

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