

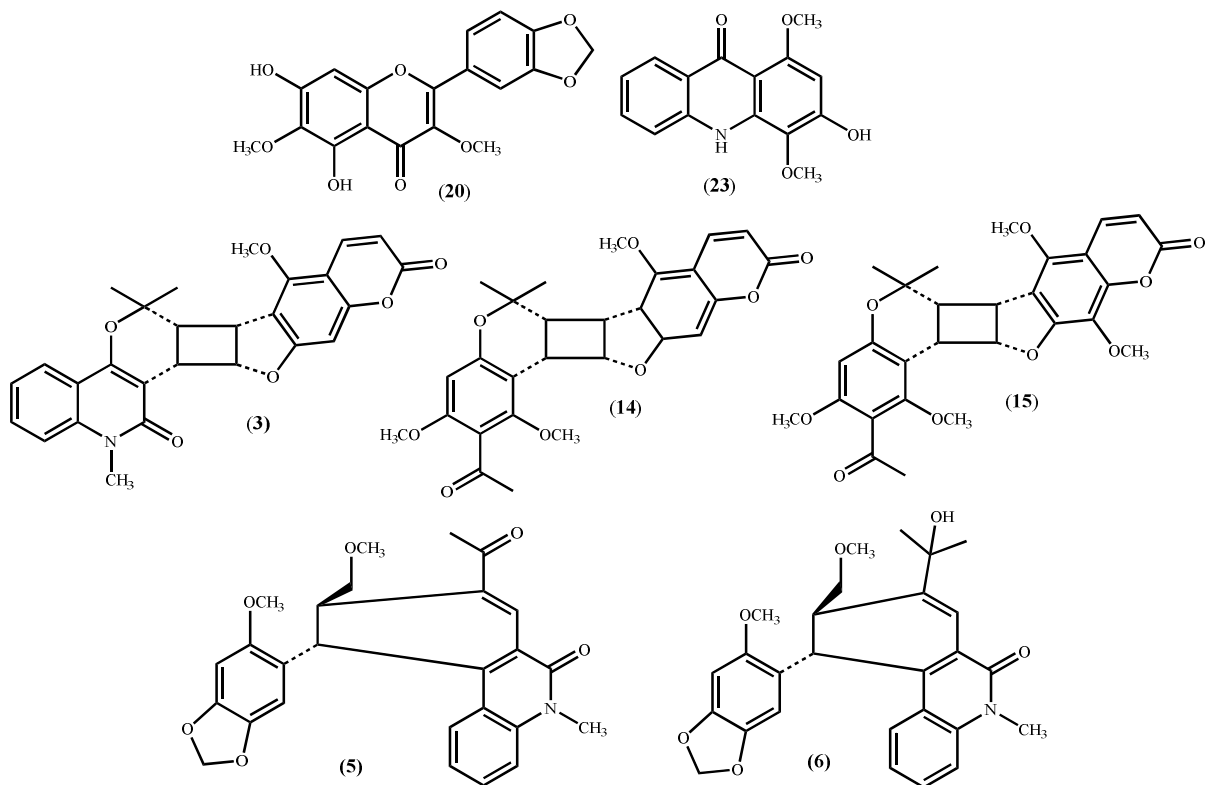
## ABSTRAK

**KERAGAMAN SENYAWA METABOLIT SEKUNDER *MELICOPE* : PEMETAAN JALUR PEMBENTUKAN SENYAWA HIBRID SIKLOADISI DAN *ADDUCT* DIELS-ALDER**

*Melicope* dikenal oleh masyarakat Indonesia sebagai “kisampang” merupakan salah satu genus yang penting dari famili Rutaceae yang tersebar di daerah tropis dan subtropis. Etnomedisin tumbuhan *Melicope*, rebusan daun digunakan masyarakat untuk pengobatan diare, demam, darah tinggi, kanker serta pengendali hama ulat dan kutu pada daun tembakau. Fitokimia tumbuhan *Melicope* menunjukkan adanya kandungan metabolit sekunder antara lain senyawa golongan alkaloid, flavonoid, kumarin, asilfloroglusinol, asam sinamat, lignan dan terpenoid. Keunikan senyawa metabolit sekunder tersebut membentuk senyawa hibrid melalui reaksi *adduct* Diels-Alder dan reaksi sikloadisi [2+2]. Senyawa hibrid melalui reaksi *adduct* Diels-Alder dan sikloadisi [2+2] belum pernah ditemukan pada tumbuhan lain. Senyawa hibrid tersebut merupakan penggabungan senyawa alkaloid-alkaloid, alkaloid-kumarin, alkaloid-asam sinamat, dan alkaloid-asilfloroglusinol.

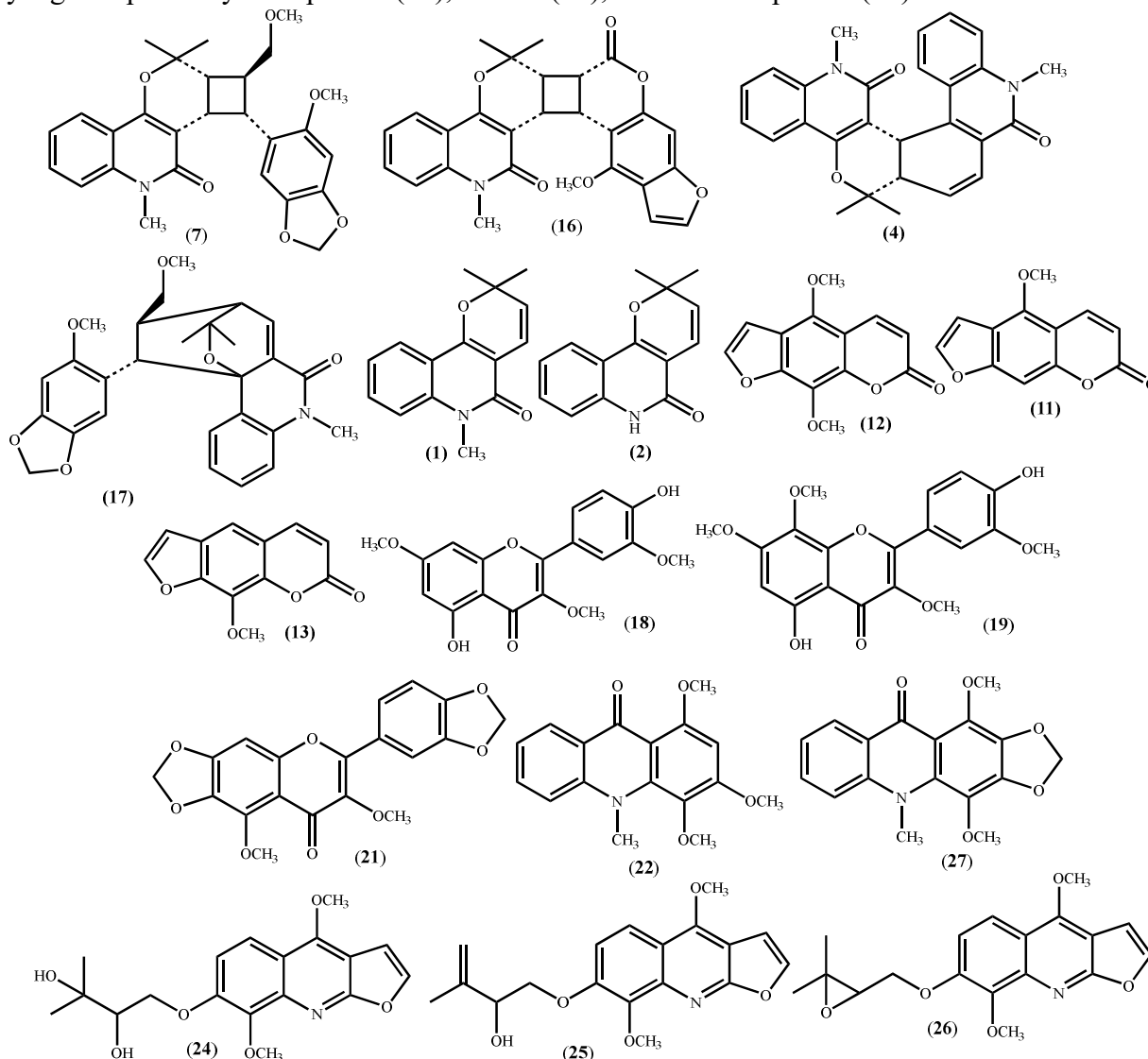
Berdasarkan latar belakang tersebut, penelitian ini melakukan kajian fitokimia *Melicope* terhadap empat spesies yaitu, *M. denhamii*, *M. glabra*, *M. quercifolia*, dan *M. xanthoxyloides*. Senyawa monomer dan senyawa hibrid hasil isolasi dilakukan uji aktivitas sitotoksik terhadap tiga sel kanker murin leukimia P-388, sel kanker rahim HeLa, dan sel kanker payudara MCF-7 untuk memperoleh hubungan antara struktur dan sitotoksisitas.

Penelitian ini telah berhasil mengisolasi 27 senyawa metabolit sekunder yang meliputi satu senyawa baru alkaloid akridon yakni melisiloidin (**23**) dan satu senyawa baru flavonol yakni meliglabranin (**20**). Tiga senyawa hibrid sikloadisi [2+2] baru yakni melikodenin J (**3**), melikuersifolin A (**14**) dan melikuersifolin B (**15**) dan dua senyawa hibrid *adduct* Diels-Alder baru yakni melikodenin L (**5**) dan melikodenin K (**6**).



Gambar-1. Senyawa baru *Melicope spp.*

Dua puluh senyawa yang telah dikenal yang meliputi empat senyawa hibrid yaitu melikodenin E (7), melikodenin F (16), melibiskuininol B (4), dan melikodenin I (17), dua senyawa turunan alkaloid kuinolon yaitu, senyawa N-metilflindersin (1) dan flindersin (2). Tiga senyawa turunan kumarin yaitu bergapten (11) isopimpinellin (12), dan santotoksin (13), dua turunan asam sinamat yaitu melikodin A (8) dan boropinol B (10), satu turunan asil floro glusinol yaitu metilevodionol (9). Tiga senyawa turunan flavonol yaitu pasipodol (18), ternatin (19), dan meliternatin (21), dua senyawa turunan akridon yaitu, 1,3,4-trimetoksi-10-metil-9-akridon (22) dan melikopidin (27), dan tiga senyawa turunan alkaloid furokuinolin yang meliputi senyawa epoksin (24), evodin (25), dan anhidroepoksin (26).

Gambar-2. Senyawa dikenal *Melicope spp.*

Penemuan tiga senyawa baru hibrid sikloadisi [2+2] yaitu melikodenin J (3), melikuersifolin A (14) dan melikuersifolin B (15) menambah keragaman senyawa hibrid *Melicope*. Senyawa melikuersifolin A (14) dan melikuersifolin B (15) dari *M. quercifolia* merupakan senyawa hibrid baru yang berasal dari penggabungan kumarin-asilfloroglusinol. Senyawa melikodenin J (3) merupakan senyawa hibrid alkaloid-kumarin yang diperoleh dari *M. denhamii*. Dua senyawa baru hibrid sikloadisi [4+2] (*adduct* Diels-Alder) yakni

melikodenin L (**5**) dan melikodenin K (**6**) yang berasal dari penggabungan alkaloid-asam sinamat dari *M. denhamii* memberi kontribusi keragaman fitokimia *Melicope*.

Sitotoksitas senyawa hasil isolasi terhadap sel P-388, HeLa, dan MCF-7 senyawa hibrid sikloadisi [2+2] memperlihatkan aktivitas yang sangat kuat terhadap sel HeLa, akan tetapi tidak aktif terhadap sel P-388 dan MCF-7. Empat senyawa hibrid *adduct* Diels-Alder dan senyawa monomer memperlihatkan aktivitas sitotoksik yang tidak aktif terhadap sel P-388, HeLa dan MCF-7. Sitotoksitas senyawa turunan flavonol memperlihatkan bahwa senyawa meliglabin (**20**) dan pasipodol (**18**) toksik terhadap sel HeLa tetapi tidak aktif terhadap sel P-388 dan MCF-7. Senyawa turunan alkaloid akridon dan furokuinolon memperlihatkan aktivitas yang tidak aktif terhadap tiga sel kanker uji kecuali senyawa 1,3,4-trimetoksi-10-metil-9-akridon (**22**) aktif terhadap sel MCF-7.

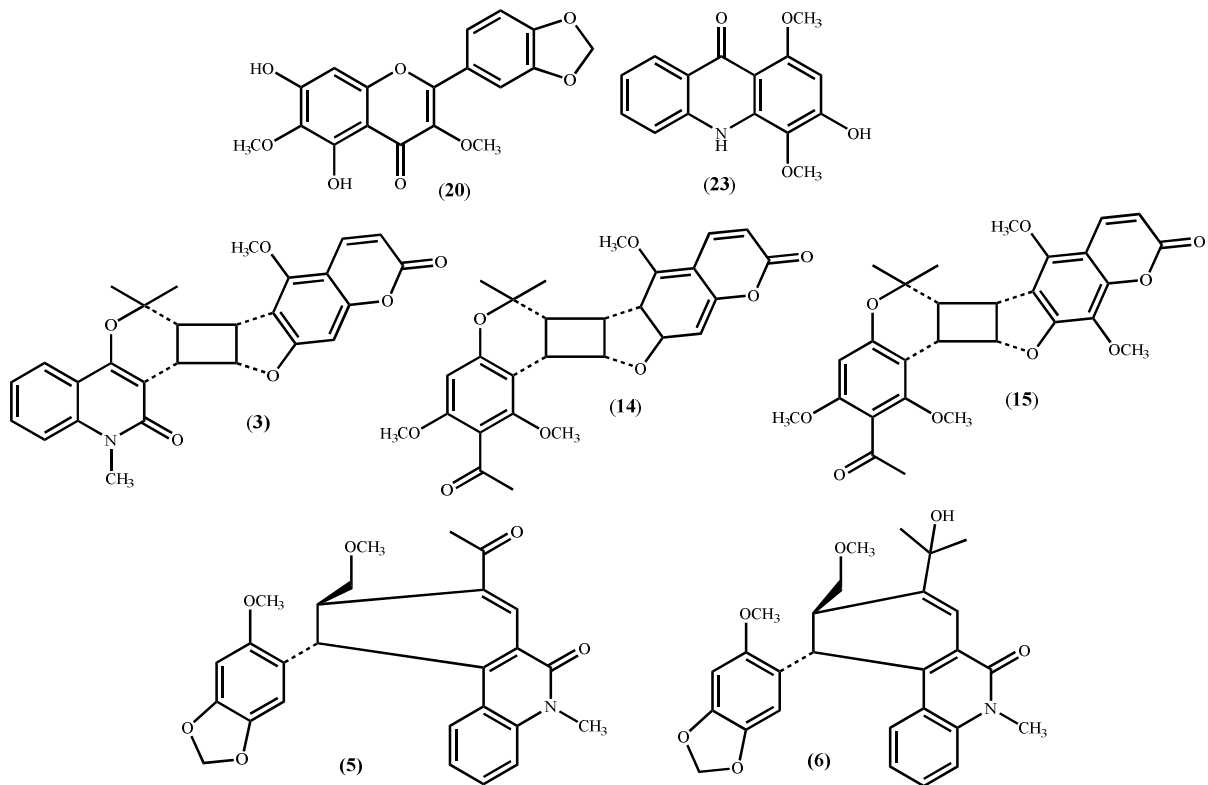
**Kata kunci** : *Melicope spp*, sikloadisi [2+2] dan [4+2], antikanker.

**ABSTRACT****DIVERSITY OF *MELICOPE* METABOLITE COMPOUNDS : MAPPING THE FORMATION OF HYBRID COMPOUND THROUGH CYCLOADITION AND ADDUCT DIELS-ALDER REACTON**

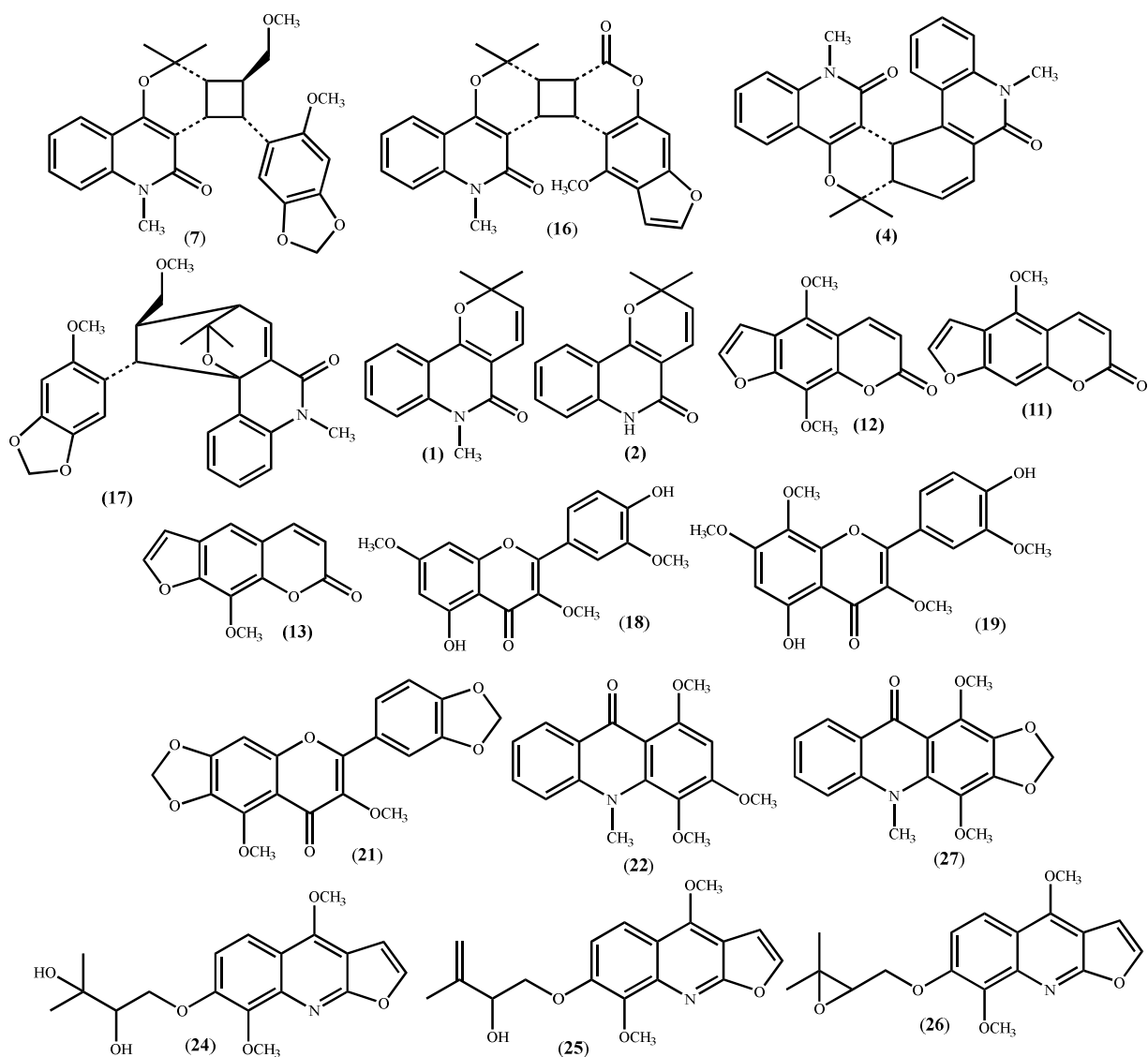
*Melicope* is known by the people of Indonesia as "kisampang" is one of the important genus of family Rutaceae which is scattered in tropical and subtropical areas. In ethnomedicin, the boiling leaves of the *Melicope* serves as a treatment of diarrhea, fever, hypertension, cancer as well as the control of caterpillars and lice in tobacco leaves. The phytochemicals of *Melicope* plants show that secondary metabolites include alkaloid, flavonoid, coumarin, acylphloroglucinol, cinnamic acid, lignan and terpenoids. The Uniqueness of the secondary metabolite compounds of *Melicope* is to form hybrid compounds through *adduct* Diels-Alder's and cycloaddition reaction. Formation of hybrid compounds through the adduct Diels-Alder and cycloaddition reaction of *Melicope* plants has never been found in other plants. Formation hybrid compounds are merger of alkaloid with coumarin, cinnamic acid, acylphloroglucinol or others. In addition to the structurally interesting to be developed, the secondary metabolite *Melicope* compounds have broad physiological functions, including, anticancer, antiviral, antioxidant, anti inflammatory and antimalaria.

Based on the background, in this research, phytochemical studies have been conducted on four *Melicope spp* species, *M. denhamii*, *M. glabra*, *M. quercifolia*, and *M. xanthoxyloides*. Monomer compounds and isolated hybrid compounds were tested for cytotoxic activity against three cancer cells including murine leukemia P-388 cancer cells, HeLa uterine cancer cells, and MCF-7 breast cancer cells to obtain a relationship between structure and cytotoxicity.

This study has succeeded in isolating 27 compounds of secondary metabolites which include one new compound of acridon alkaloids namely melisiloidin (**23**) and one new flavonol compound namely meliglabranin (**20**). Three new cycloaddition [2+2] hybrid compounds namely melicodenin J (**3**), meliquersifolins A (**14**) and meliquersifolins B (**15**) and two new adduct Diels-Alder hybrid compounds namely melicodenin L (**5**) and melicodenin K (**6**)

Gambar-1. Senyawa baru *Melicope* spp.

Twenty known compounds which include four hybrid compounds namely melicodenin E (7), melicodenin F (16), melicobisquinolinone B (4), and melicodenin I (17), two quinolone alkaloid derivatives namely, N-methylflindersine compound (1) and flindersine (2), three coumarin-derived compounds namely bergaptene (11) isopimpinellin (12), and xanthotoxine (13), two derivatives of cinnamic acid namely melicodin A (8) and boropinol B (10), one acylphloroglucinol derivative, methylevodionol (9), three flavonol-derived compounds namely pacipodol (18), ternatin (19), and meliternatin (21), two acridone-derived compounds namely, 1,3,4-Trimethoxy-10-methyl-9-acridone (22) and melicopidine (27), and the three derivative compounds of furoquinolin alkaloids include epoxine compounds (24), evodin (25), and anhydroepoxine (26).

Gambar-2. Senyawa telah dikenal *Melicope* spp.

The discovery of three new [2+2] cycloaddition hybrid compounds, namely melikodenin J (**3**), meliquersifolins A (**14**) and meliquersifolins B (**15**) add to the diversity of the *Melicope* hybrid compound. Meliquersifolins A (**14**) and meliquersifolins B (**15**) from *M. quercifolia* is a new hybrid compound derived from the combination of coumarin- acylphloroglucinol. Melikodenin J (**3**) is a hybrid alkaloid-coumarin compound derived from a N-methylflindersine (**1**) with bergaptene (**11**). Meliquersifolins A (**14**) and meliquersifolins B (**15**) are a hybrid compound with the formation of a new skeleton derived from the merger of coumarin- acylphloroglucinol. Both of these compounds are a new compound of [2+2] cycloaddition and the first time found in *Melicope* plants. Melikodenin L (**5**) and melikodenin K (**6**) are *adduct* Diels-Alder compounds between melicodin A (**8**) double bonds with  $\alpha$ ,  $\beta$ -ketones unsaturated N-methylflindersine compound (**1**).

Cytotoxicity test compound results of isolation against murine cancer cells P-388, HeLa uterine cancer cells, and breast cancer cells MCF-7 showed that cycloaddition [2+2] hybrid compounds had very strong cytotoxic activity against HeLa cells, but not active against P-388 and MCF-7 cells. Four adduct Diels-Alder hybrid and monomer compounds showed inactive cytotoxic activity against P-388, HeLa, and MCF-7 cells. The cytotoxicity of flavonol

derivatives showed that meliglabrin (**20**) and pacipodol (**18**) were toxic to HeLa cells but inactive against P-388 and MCF-7 cells. The alkaloid derivatives of acridone and furoquinolinones showed inactive activity against three cancer cells, except for 1,3,4-trimethoxy-10-methyl-9-acridone compounds (**22**) which were active against MCF-7 cells.

**Keyword:** *Melicope spp*, cycloaddition [2+2] and [4+2], anticancer.