Bioorganic & Medicinal Chemistry Letters xxx (2014) xxx–xxx

Contents lists available at ScienceDirect

Bioorganic & Medicinal Chemistry Letters

journal homepage: www.elsevier.com/locate/bmcl

Design, synthesis and antimycobacterial activity evaluation of natural oridonin derivatives

Shengtao Xu [a,b,†], Dahong Li [a,b,c,†], Lingling Pei [a,b], Hong Yao [a], Chengqian Wang [a], Hao Cai [a,b], Hequan Yao [a,b], Xiaoming Wu [a,b], Jinyi Xu [a,b,*]

[a] State Key Laboratory of Natural Medicines, China Pharmaceutical University, 24 Tong Jia Xiang, Nanjing 210009, China
[b] Department of Medicinal Chemistry, China Pharmaceutical University, 24 Tong Jia Xiang, Nanjing 210009, China
[c] Key Laboratory of Structure-Based Drug Design & Discovery of Ministry of Education and School of Traditional Chinese Materia Medica, Shenyang Pharmaceutical University, 103 Wen Hua Road, Shenyang 110016, China

ARTICLE INFO

Article history:
Received 26 January 2014
Revised 20 April 2014
Accepted 29 April 2014
Available online xxxx

Keywords:
Oridonin
trans-Cinnamic acid
Tuberculosis
Antimycobacterial activity

ABSTRACT

In an effort to develop novel potent antitubercular drugs, thirty-one oridonin derivatives were designed and prepared. All the compounds obtained were screened for their in vitro activities against *Mycobacterium phlei*, *Mycobacterium smegmatis* and *Mycobacterium marinum*. Among them, thirteen compounds showed significant inhibitory activity against *M. phlei* with MICs less than 2 μg/mL. Compounds **2k**, **8d**, **10c**, **10d** containing *trans*-cinnamic acid moiety were the most potent (MIC = 0.5 μg/mL), comparable to the well-known antitubercular drug streptomycin. The preliminary structure–activity relationships (SARs) were also analyzed.

It is estimated that one-third part of the world population was infected with the tubercle bacillus, and 8 million new cases emerged annually.[1] The World Health Organization (WHO) reported that nearly 3 million deaths which represent the largest number of incidence of human deaths were directly attributable to infection with the bacillus.[2] In the past decade, the incidence of tuberculosis infection has rapidly increased, the long treatment duration, emergence of drug-resistant strains of *Mycobacterium tuberculosis*, co-morbidity with HIV-AIDS and lack of new antitubercular drugs have increased the pressure on current chemotherapy regimes.[3] The urgent need for the development of novel drugs to reduce the global burden of tuberculosis has been well documented,[4] unfortunately, new drugs against tuberculosis have not been developed in over 30 years.

Natural products currently play an important role in the chemotherapy of tuberculosis,[5] for example, streptomycin, capreomycin, cycloserine, semisynthetic rifamycin analogues rifampicin, rifabutin, and rifapentine are used as either front-line or second line drugs. These natural products as well as their semisynthetic analogues have indicated that inhibitory activity against *M. tuberculosis* is widespread in nature. Now, there is a re-emerging interest in natural products as being able to provide novel template for the development of new drugs and being particularly suitable as antibacterial leads.[6] *Isodon* (formally *Rabdosia*) is a cosmopolitan and important genus of the Labiatae family, and *Isodon* diterpenoids have attracted considerable attention as antibacterial, anti-inflammatory and anti-tumor agents.[7] It is known that oridonin (**1**), isolated from the herb *Isodon rubescens* that is always used in China for the treatment of respiratory, inflammation and bacterial infection, was found to exhibit antibacterial activity against Gram-positive bacteria as early as in 1976.[8] However, until now, there has been no report on the activity of oridonin or its derivatives against *M. tuberculosis*.

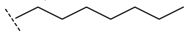
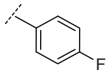
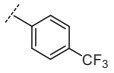
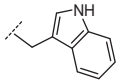
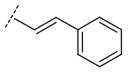
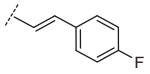
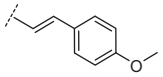
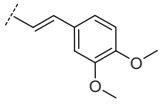
Herein, we wish to report natural oridonin and its derivatives as new promising template for further elaboration as antitubercular drugs.

To evaluate the potential as a lead for the development of new drug against tuberculosis, oridonin was initially evaluated for its antitubercular activities against *Mycobacterium phlei*, *Mycobacterium smegmatis* and *Mycobacterium marinum*. It was observed that **1** showed moderate activity with an MIC value of 16 μg/mL (The MIC is defined as the minimum concentration of compound required to inhibit the visible growth of bacteria) against *M. phlei* (Table 1). This positive result encourages us to further optimize the structure of oridonin for enhancing its activity. Structurally, oridonin is a highly oxygenated 7,20-epoxy-*ent*-kaurane-type

* Corresponding author. Tel.: +86 25 83271299; fax: +86 25 83302827.
E-mail address: jinyixu@china.com (J. Xu).
† These authors contributed equally to this work.

http://dx.doi.org/10.1016/j.bmcl.2014.04.119
0960-894X/

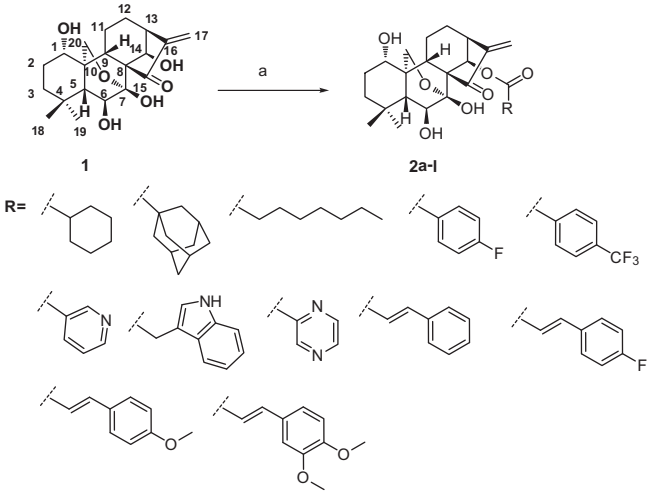
Table 1
Structures and activities of oridonin derivatives (μg/mL)

Compd	R	MP[a]	MS[b]	MM[c]	Clog*P*[d]	PSA[d] (Å^2)
1	—	16	>64	>64	−0.62	107.22
2a		8	ND[e]	ND	2.31	113.29
2b		16	ND	ND	2.93	113.29
2c		2	16	16	3.45	113.29
2d		32	ND	ND	2.14	113.29
2e		16	ND	ND	2.88	113.29
2f		16	ND	ND	0.66	125.65
2g		32	ND	ND	1.89	125.32
2h		4	32	32	0.78	138.01
2i		1	8	8	2.45	113.29
2j		2	4	8	2.59	113.29
2k		0.5	4	4	2.37	122.52
2l		1	8	16	2.11	131.75
SM[f]		0.5	0.125	0.5	—	—

[a] *Mycobacterium phlei* (ATCC 355).
[b] *Mycobacterium smegmatis* (ATCC19420).
[c] *Mycobacterium marinum* (ATCC 927).
[d] Calculated using chem draw ultra 12.0.
[e] ND = Not determined.
[f] Streptomycin.

diterpenoid that features densely functionalized hydroxyl groups. Due to the fact that the cell wall of mycobacteria contain lipophilic substances, more lipophilic substances are likely to penetrate more easily into the cell. It has been reported that the modulation of Clog*P* values often contributes better antitubercular activity for some compounds.[9] So, a small library of 14-*O*-derivatives of oridonin (**2a**–**l**) was constructed by selective introduction of a series of different side chains into the 14-*O*-position of oridonin to reduce the number of hydroxyl groups and to increase the lipophilicity. As shown in Scheme 1, due to the steric effect, the 14-hydroxy appears to be the most reactive, the 14-*O*-derivatives of oridonin could be mainly obtained by accurate control of the reaction time and stoichiometry. The treatment of oridonin with corresponding acids in the presence of DMAP/EDCI in dry dichloromethane gave corresponding compounds **2a**–**l** in 47–89% yields.[10]

Lipophilicity of the newly synthesized derivatives **2a**–**l** is expressed in terms of Clog*P* values. As shown in Table 1, a remarkable improvement in lipophilicity of the synthesized oridonin derivatives was evidenced by Clog*P* values (0.66–3.45), relative to the parent oridonin (−0.62). The inhibitory activity of the derivatives against *Mycobacterium phlei* was evaluated using the Microplate Alamar Blue Assay (MABA). As shown in Table 1, some of the 14-*O*-dervatives of oridonin (**2a**, **2c**, **2h**, **2i**, **2j**, **2k**, **2l**) with their MIC values between 0.5 and 8 μg/mL exhibited better activity than that of oridonin (16 μg/mL). To our delight, four compounds (**2i**–**l**) obtained by conjugation with various *trans*-cinnamic acid displayed comparable activity (MIC = 0.5–2 μg/mL) to positive drug streptomycin (MIC = 0.5 μg/mL).



Scheme 1. Synthesis of oridonin derivatives **2a**–**l**. Reaction conditions: (a) RCOOH, EDCI, DMAP, rt, overnight, 47–89%.

It is traditionally known that *trans*-cinnamic acid (**3**) possesses antimycobacterial activity[11] and has also been proven to have synergistic action when tested with clinically used drugs.[12] In recent years, *trans*-cinnamic acid derivatives have attracted much attention, for example, curcumin (**4**) (Fig. 1), a polyphenolic compound found in turmeric and piplartin (**5**), an alkaloid isolated from *Piper tuberculatum* have been widely investigated and their anti-tumor, antimicrobial properties have been well established.[13] More importantly, superior intracellular and in vivo activity of a cinnamyl-rifamycin derivative (**6**) in comparison with rifamycin was observed when tested against 20 susceptible and MDR *M. tuberculosis* strains.[14]

Subsequently the 14-*O*-dervatives of oridonin exhibiting good antimycobacterial activity were further evaluated against *Mycobacterium smegmatis* and *Mycobacterium marinum*, the data

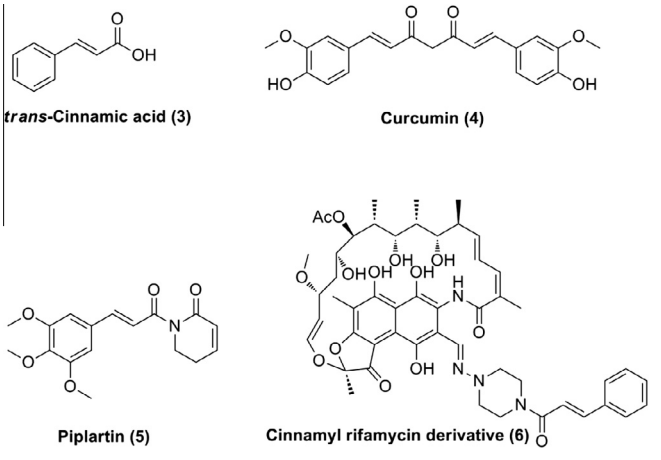
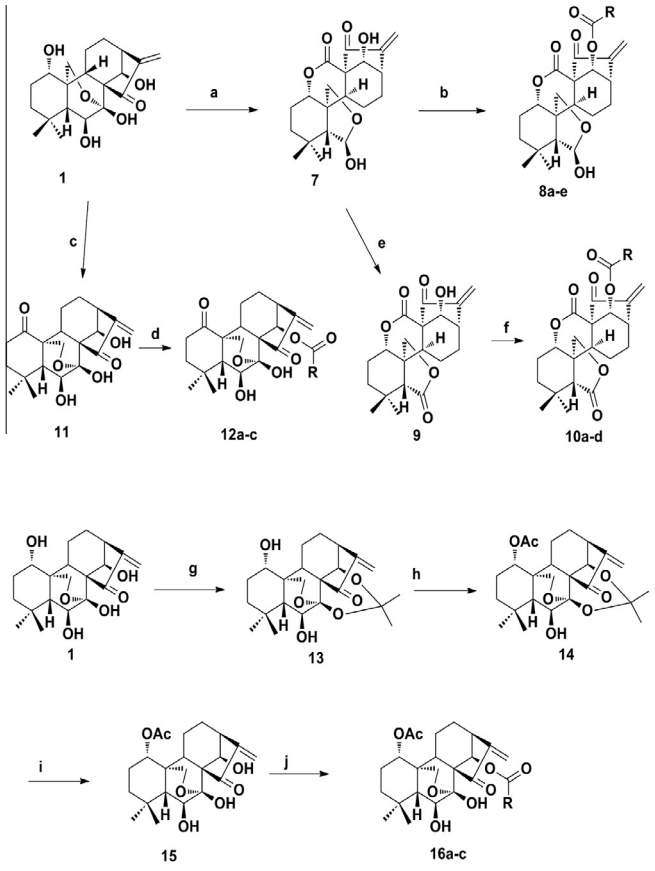


Figure 1. *trans*-Cinnamic acid (**3**), curcumin (**4**), piplartin (**5**) and cinnamyl-rifamycin derivative (**6**).

revealed that these derivatives also have potent activity against *M. smegmatis* and *M. marinum* (MICs: 4–32 μg/mL), although they are less active than the positive drug streptomycin (MIC: 0.125 μg/mL) against *M. smegmatis*.

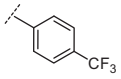
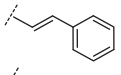
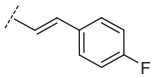
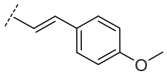
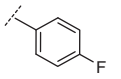
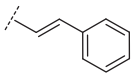
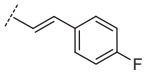
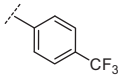
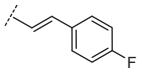
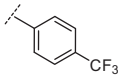
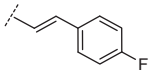
In our initial modification research, introduction of *trans*-cinnamic moiety into oridonin framework was achieved successfully, 8- to 32-fold lower MICs than that of oridonin was observed in the derivatives **2i–l** in the preliminary screening against *M. phlei*. In order to explore whether other diterpenoids possess antimycobacterial activity, a series of oridonin analogues were designed and then their *trans*-cinnamic derivatives were also synthesized. As shown in Scheme 2, treatment of **1** with sodium periodate in water gave ester **7** in 98% yield, oxidation of **1** and **7** with Jones reagent at 0 °C afforded corresponding ketones **11** and **9** in yields of 94% and 92%, respectively. Treatment of **1** with 2,2-dimethoxypropane in the presence of TsOH in acetone provided ketal **13** in 97% yield; compound **13** upon reaction with Ac_2O/DMAP/TEA led to acetylated compound **14** in the yield of 94%; deprotection of **14** with 10% HCl gave the corresponding alcohol **15** in almost quantitative yield. Since 14-*O*-derivatives of **1** exhibited stronger activity than parent compound, we continued to investigate whether 14-*O*-derivatives of these tetracyclic diterpenoids also possess improved potency, especially when conjugated with *trans*-cinnamic acid.[15]

Susceptibility of *M. phlei* to the synthesized compounds was initially tested by determining the MIC (Table 2). Three of four oridonin analogues (**7**, **9**, **11**) showed the same activity (MICs: 8–32 μg/mL) as that of oridonin except for compound **15**, which exhibited an MIC of 1 μg/mL, 16-fold lower than that of oridonin. As shown in Table 2, the modification on the C-1 position of oridonin may have the potential to influence its antimicrobial activity, for example, acetylated oridonin at 1-hydroxy position (**15**) which is also a naturally occurring compound named lasiokaurin[16] exhibited a good MIC value of 1 μg/mL, while oxidized oridonin derivative (**11**) showed somewhat decline in activity (8 μg/mL). Gratifyingly, when *trans*-cinnamic acid was used as coupling partner, the same trends were also observed in the derivatives **8c–e** and **10c–d** (MICs: 0.5–2 μg/mL). In these two series of *trans*-cinnamic acid derivatives, compounds **8d**, **10c** and **10d** were found



Scheme 2. Synthesis of oridonin analogues and their derivatives. Reaction conditions: (a) $NaIO_4$, H_2O, rt, 98%; (b) RCOOH, EDCI, DMAP, rt, overnight, 51–83%; (c) Jones reagents, acetone, 0 °C, 10 min, 94%; (d) RCOOH, EDCI, DMAP, rt, overnight, 68–91%; (e) Jones reagents, acetone, 0 °C, 15 min, 92%; (f) RCOOH, EDCI, DMAP, rt, overnight, 41–78%; (g) DMP, TsOH, acetone, 70 °C, 10 min, 97%; (h) Ac_2O, DMAP, TEA, DCM, rt, 3 h, 94%; (i) 10% HCl, THF, 0.5 h, 97%; (j) RCOOH, EDCI, DMAP, rt, overnight, 57–91%.

Table 2
Structures and activities of oridonin analogues (μg/mL)

Compd	R	MP[a]	MS[b]	MM[c]	Clog*P*[d]	PSA[d](Å^2)
7	—	32	ND[e]	ND	0.53	93.06
8a		32	ND	ND	1.32	99.13
8b		8	16	16	3.79	99.13
8c		2	16	32	3.41	99.13
8d		0.5	16	16	3.56	99.13
8e		2	16	32	3.33	108.36
9	—	16	ND	ND	0.20	89.9
10a		2	64	64	1.06	95.97
10b		2	16	32	3.38	95.97
10c		0.5	4	4	3.23	95.97
10d		0.5	4	4	2.93	95.97
11	—	8	ND	ND	0.05	104.06
12a		16	ND	ND	2.95	110.13
12b		16	ND	ND	3.09	110.13
12c		8	16	64	3.16	110.13
15	—	1	16	32	0.25	113.29
16a		8	ND	ND	3.18	119.36
16b		16	ND	ND	3.76	119.36
16c		8	16	64	3.47	119.36
SM[f]		0.5	0.125	0.5	—	—

[a] *Mycobacterium phlei* (ATCC 355).
[b] *Mycobacterium smegmatis* (ATCC19420).
[c] *Mycobacterium marinum* (ATCC 927).
[d] Calculated using chem draw ultra 12.0.
[e] ND = Not determined.
[f] Streptomycin.

to possess most potent activity (0.5 μg/mL), which were 64- and 32-fold lower MICs than that of their parent compounds (**7** and **9**), respectively. However, when *trans*-cinnamic acid was introduced to oxidized oridonin (**11**), no increase in antimicrobial activity was observed in derivative **12c**. To our surprise, although parent compound (**15**) was found to show good antimycobacterial activity, its 14-*O*-derivatives (**16a**–**c**) had no decrease in the MIC values.

Next, the compounds with potent activity against *M. phlei* were further tested against *M. smegmatis* and *M. marinum*. The data revealed that the cinnamyl-oridonin derivatives also have potent activities against *M. smegmatis* and *M. marinum*, but they are generally less active than the positive drug streptomycin.

In conclusion, it is the first report on the antimycobacterial activity of natural oridonin and its semisynthetic analogues. The preliminary results showed that these compounds may be regarded as the interesting leads for the further design and synthesis of *M. tuberculosis* inhibitors. Furthermore, the antimycobacterial activity of oridonin and its derivatives could be greatly increased by the introduction of *trans*-cinnamic moiety. As a result, cinnamyl-oridonin derivatives **2k**, **8d**, **10c** and **10d** displayed the promising antimycobacterial activity compared to the positive drug streptomycin. The preliminary SARs obtained suggest that the antimycobacterial activity may be influenced by the substitutions at the C-1 position of oridonin.

Based on the preliminary investigation results, our efforts are now focused on the modification and understanding the mode of action of these novel template molecules. It is expected that the biological results described and the further modification studies will expedite the development of new chemotherapeutic agents for the clinical intervention of tubercular disease.

Acknowledgments

This study was supported by grants from the National Natural Science Foundation (Nos. 30973610; 81373280), the Young Teachers' Scientific Research Fund Project of Shenyang Pharmaceutical University (QNJJ 2013501) and the Project Program of State Key Laboratory of Natural Medicines, China Pharmaceutical University (No. SKLNMZZCX201404).

Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.bmcl.2014.04.119.

References and notes

1. (a) Dye, C.; Glaziou, P.; Floyd, K.; Raviglione, M. *Annu. Rev. Public Health* **2013**, *34*, 271; (b) Dye, C.; Williams, B. G. *Science* **2010**, *328*, 856; (c) Koul, A.; Arnoult, E.; Lounis, N.; Guillemont, J.; Andries, K. *Nature* **2011**, *469*, 483.
2. World Health Organization, Tuberculosis Fact Sheet N°104, Updated October 2013; please see: http://www.who.int/mediacentre/factsheets/fs104/en/.
3. (a) Gandhi, N. R.; Nunn, P.; Dheda, K.; Schaaf, H. S.; Zignol, M.; van Soolingen, D.; Jensen, P.; Bayona, J. *Lancet* **2010**, *375*, 1830; (b) Boehme, C. C.; Nabeta, P.; Hillemann, D.; Nicol, M. P.; Shenai, S.; Krapp, F.; Allen, J.; Tahirli, R.; Blakemore, R.; Rustomjee, R.; Milovic, A.; Jones, M.; O'Brien, S. M.; Persing, D. H.; Ruesch-Gerdes, S.; Gotuzzo, E.; Rodrigues, C.; Alland, D.; Perkins, M. D. N. *Engl. J. Med.* **2010**, *363*, 1005.
4. (a) Andries, K.; Verhasselt, P.; Guillemont, J.; Göhlmann, H. W.; Neefs, J. M.; Winkler, H.; van Gestel, J.; Timmerman, P.; Zhu, M.; Lee, E.; Williams, P.; de Chaffoy, D.; Huitric, E.; Hoffner, S.; Cambau, E.; Truffot-Pernot, C.; Lounis, N.; Jarlier, V. *Science* **2005**, *307*, 223; (b) Tripathi, R. P.; Tewari, N.; Dwivedi, N.; Tiwari, V. K. *Med. Res. Rev.* **2005**, *25*, 93; (c) Corbett, E. L.; Watt, C. J.; Walker, N.; Maher, D.; Williams, B. G.; Raviglione, M. C.; Dye, C. *Arch. Intern. Med.* **2003**, *163*, 1009; (d) Stover, C. K.; Warrener, P.; VanDevanter, D. R.; Sherman, D. R.; Arain, T. M.; Langhorne, M. H.; Anderson, S. W.; Towell, J. A.; Yuan, Y.; McMurray, D. N.; Kreiswirth, B. N.; Barry, C. E.; Baker, W. R. *Nature* **2000**, *405*, 962.
5. (a) Copp, B. R. *Nat. Prod. Rep.* **2003**, *20*, 535; (b) Copp, B. R.; Pearce, A. N. *Nat. Prod. Rep.* **2007**, *24*, 278; (c) Okunade, A. L.; Elvin-Lewis, M. P. F.; Lewis, W. H. *Phytochemistry* **2005**, *65*, 1017; (d) Bueno, J.; Coy, E. D.; Stashenko, E. *Rev. Esp. Quimioter.* **2011**, *24*, 175; (e) Pauli, G. F.; Case, R. J.; Inui, T.; Wang, Y.; Cho, S.; Fischer, N. H.; Franzblau, S. G. *Life Sci.* **2005**, *78*, 485.
6. (a) Newman, D. J.; Craggand, G. M.; Snader, K. M. *Nat. Prod. Rep.* **2000**, *17*, 215; (b) Koehna, F. E.; Carter, G. T. *Nat. Rev. Drug Disc.* **2005**, *4*, 206; (c) Butler, M. S.; Buss, A. D. *Biochem. Pharmacol.* **2006**, *71*, 919; (d) Stavrakov, G.; Philipova, I.; Valcheva, V.; Momekov, G. *Bioorg. Med. Chem. Lett.* **2013**. http://dx.doi.org/10.1016/j.bmcl.2013.11.050; (e) Nagai, K.; Koyama, N.; Sato, N.; Yanagisawa, C.; Tomoda, H. *Bioorg. Med. Chem. Lett.* **2012**, *22*, 7739.
7. Sun, H. D.; Huang, S. X.; Han, Q. B. *Nat. Prod. Rep.* **2006**, *23*, 673.
8. Fujita, E.; Nagao, Y.; Kaneko, K.; Nakazawa, S.; Kuroda, H. *Chem. Pharm. Bull.* **1976**, *24*, 2118.
9. (a) Rodrigues, M. O.; Cantos, J. B.; D'Oca, C. R.; Soares, K. L.; Coelho, T. S.; Piovesan, L. A.; Russowsky, D.; da Silva, P. A.; D'Oca, M. G. *Bioorg. Med. Chem.* **2013**, *21*, 6910; (b) Gonec, T.; Kos, J.; Zadrazilova, I.; Pesko, M.; Keltosova, S.; Tengler, J.; Bobal, P.; Kollar, P.; Cizek, A.; Kralova, K.; Jampilek, J. *Bioorg. Med. Chem.* **2013**, *21*, 6531; (c) Pinheiro, M.; Arêde, M.; Caio, J. M.; Moiteiro, C.; Lúcio, M.; Reis, S. *Eur. J. Pharm. Biopharm.* **2013**, *85*, 593.
10. Analytical data for the representative compounds: (**2k**): 75% as white solid, mp 175–177 °C; ^{1}H NMR ($CDCl_3$, 300 MHz): δ (ppm) 7.59, 6.20 (dd, $J_A = J_B = 15.9$ Hz, each 1H), 7.44 (d, $J = 8.7$ Hz, 2H), 6.89 (d, $J = 8.7$ Hz, 2H), 6.21 (m, 2H), 5.93 (s, 1H), 5.49 (s, 1H), 4.42 (s, 1H), 4.09, 4.35 (dd, $J_A = J_B = 9.6$ Hz, each 1H), 3.86 (s, 3H), 3.79 (m, 1H), 3.53 (m, 1H), 3.27 (m, 1H), 2.63 (m, 1H), 2.38 (m, 1H), 2.04 (m, 1H), 1.80 (m, 2H), 1.71 (m, 5H), 1.54 (m, 1H), 1.11 (s, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ (ppm) 206.3, 165.0, 161.4, 149.4, 145.8, 129.6, 126.0, 119.7, 113.9, 113.5, 95.8, 76.1, 72.9, 62.9, 61.4, 59.4, 54.9, 54.1, 40.9, 40.8, 38.2, 33.3, 32.0, 30.0, 29.5, 21.1, 19.2; MS (ESI) m/z: 525.3 $[M+H]^+$; HR-MS (ESI, M+H) m/z: calcd for $C_{30}H_{37}O_8$: 525.2483, found 525.2493.
11. (a) Naz, S.; Ahmed, S.; Ajaz-Rasool, S. A.; Asad-Sayeed, S. A.; Siddiqi, R. *Microbiol. Res.* **2006**, *161*, 43; (b) Carvalho, S. A.; da Silva, E. F.; de Souza, M. V. N.; Lourenco, M. C. S.; Vicente, F. R. *Bioorg. Med. Chem. Lett.* **2008**, *18*, 538; (c) Koumba Yoya, G.; Bedos-Belval, F.; Constant, P.; Duran, H.; Daffé, M.; Baltas, M. *Bioorg. Med. Chem. Lett.* **2009**, *19*, 341; (d) De, P.; Koumba Yoya, G.; Constant, P.; Bedos-Belval, F.; Duran, H.; Saffon, N.; Daffé, M.; Baltas, M. *J. Med. Chem.* **2011**, *54*, 1449; (e) Kakwani, M. D.; Palsule Desai, N. H.; Lele, A. C.; Ray, M.; Rajan, M. G.; Degani, M. S. *Bioorg. Med. Chem. Lett.* **2011**, *21*, 6523.
12. Rastogi, N.; Goh, K. S.; Horgen, L.; Barrow, W. W. *FEMS Immunol. Med. Microbiol.* **1998**, *21*, 149.
13. (a) Bezerra, D. P.; Castro, F. O.; Alves, A. P.; Pessoa, C.; Moraes, M. O.; Silveira, E. R.; Lima, M. A. S.; Elmiro, F. J.; Costa-Lotufo, L. V. *Braz. J. Med. Biol. Res.* **2006**, *39*, 801; (b) Leal, P. F.; Braga, M. E. M.; Sato, D. N.; Carvalho, J. E.; Marques, M. O. M.; Meireles, M. A. A. *J. Agric. Food. Chem.* **2003**, *51*, 2520; (c) Changtam, C.; Hongmanee, P.; Suksamram, A. *Eur. J. Med. Chem.* **2010**, *45*, 4446.
14. Reddy, V. M.; Nadadhur, G.; Daneluzzi, D.; Dimova, V.; Gangadharam, P. R. *Antimicrob. Agents Chemother.* **1995**, *39*, 2320.
15. Wang, L.; Li, D. H.; Xu, S. T.; Cai, H.; Yao, H. Q.; Zhang, Y. H.; Jiang, J. Y.; Xu, J. Y. *Eur. J. Med. Chem.* **2012**, *52*, 242. Analytical data for the representative compounds: (**8d**): 68% as white solid, mp 148–150 °C; ^{1}H NMR ($CDCl_3$, 300 MHz): δ (ppm) 7.60, 6.28 (dd, $J_A = J_B = 16.2$ Hz, each 1H), 7.48 (m, 2H), 7.04 (t, $J = 11.4$ Hz, 2H), 6.24 (s, 1H), 5.80 (s, 1H), 5.57 (s, 1H), 5.33 (d, $J = 1.2$ Hz, 1H), 4.60 (m, 1H), 3.96, 4.08 (dd, $J_A = J_B = 9.6$ Hz, each 1H), 3.24 (d, $J = 9.3$ Hz, 1H), 2.78 (m, 2H), 2.61 (m, 1H), 2.04 (m, 2H), 1.90 (s, 1H), 1.71 (m, 4H), 1.54 (m, 1H), 1.15 (s, 3H), 1.01 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ (ppm) 196.2, 165.6, 165.3, 147.3, 144.7, 129.8, 129.8, 119.8, 116.2, 115.6, 115.3, 101.2, 74.0, 73.6, 59.7, 53.3, 49.5, 48.0, 40.4, 36.6, 32.4, 30.5, 29.2, 22.8, 22.5, 19.3; MS (ESI) m/z: 511.3 $[M+H]^+$; HR-MS (ESI, M+H) m/z: calcd for $C_{29}H_{32}FO_7$: 511.2127, found 511.2136. (**10d**): 64% as white solid, mp 136–138 °C; ^{1}H NMR ($CDCl_3$, 300 MHz); δ (ppm) 7.62, 6.27 (dd, $J_A = J_B = 16.2$ Hz, each 1H), 7.47 (t, $J = 8.4$ Hz, 2H), 7.07 (t, $J = 8.4$ Hz, 2H), 6.18 (s, 1H), 5.93 (s, 1H), 5.62 (s, 1H), 4.64 (m, 1H), 4.31, 4.02 (dd, $J_A = J_B = 9.3$ Hz, each 1H), 3.27 (d, $J = 9.3$ Hz, 1H), 2.60 (m, 1H), 2.06 (m, 2H), 1.93 (s, 2H), 1.74 (m, 4H), 1.52 (m, 1H), 1.26 (s, 3H), 1.22 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 197.2, 189.4, 175.2, 166.0, 165.7, 162.4, 146.9, 145.4, 130.3, 130.1, 121.4, 116.2, 115.8, 74.8, 73.4, 71.3, 59.4, 50.7, 47.5, 45.9, 40.4, 36.3, 33.0, 32.2, 29.4, 23.5, 23.0, 19.1; MS (ESI) m/z: 509.2 $[M+H]^+$, 526.2 $[M+NH_4]^+$; HR-MS (ESI, M+H) m/z: calcd for $C_{29}H_{30}FO_7$: 509.1970, found 509.1966.
16. Fujita, E.; Nagao, Y.; Node, M.; Kaneko, K.; Nakazawa, S.; Kuroda, H. *Experientia* **1976**, *32*, 203.