ChemComm

Accepted Manuscript

This article can be cited before page numbers have been issued, to do this please use: M. Gholshani, M. Khoobi, N. Jalalimanesh, F. Jafarpour and A. Ariafard, *Chem. Commun.*, 2017, DOI: 10.1039/C7CC02107K.

ROYAL SOCIETY OF CHEMISTRY

rsc.li/chemcomm

ROYAL SOCIETY OF CHEMISTRY View Article Online
DOI: 10.1039/C7CC02107K

Journal Name

COMMUNICATION

Transition-Metal-Free Fast Track to Flavones and 3-Arylcoumarins

Mostafa Golshani,[a,b] Mehdi Khoobi,[a,c]* Nafiseh Jalalimanesh,[b] Farnaz Jafarpour[b]* and Alireza Ariafard[d,e]

Received 00th January 20xx,
Accepted 00th January 20xx

DOI: 10.1039/x0xx00000x

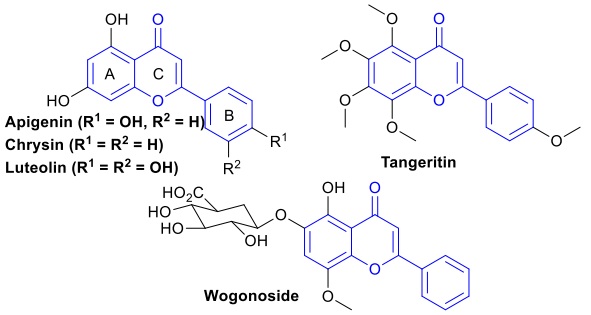
www.rsc.org/

Highly regioselective and transition-metal free one-pot arylation of chromenones with arylboronic acids has been achieved employing $K_2S_2O_8$. The procedure consists of a sequence of some reactions including arylation/decarboxylation cascade and proceeds well in aqueous media to afford biologically interesting flavones and 3-aryl coumarins. This method exhibited excellent selectivity and functional group tolerance under mild conditions. The reaction also showed perfect efficacy for the preparation of styryl coumarin.

Natural and synthetic compounds featuring a 2-arylchromone (flavone) scaffold, are proved to have a positive effect on diseases related to oxidative stress, inflammatory and neurodegenerative disorders, diabetes mellitus, peptic ulcers, cancer and so on (Scheme 1).[1] They also exhibit anti-microbial, anti-HIV, anti-oxidant, anti-platelet and vasorelaxing properties.[1] The widespread use of flavones in pharmaceutical as well as food industry have ensured a continuous demand for direct and efficient synthesis of these structural motifs. Although robust methods including chalcone and diketone route have been established in this regard,[2] significant effort have been devoted toward more feasible transition metal (TM)-catalyzed direct instalment of aryls onto an extant enone nucleus as an alternative synthetic route with less functional group limitations.[3] Thus far, regioselective direct arylation of chromones via TM-catalyzed coupling reactions using haloarenes[3c-d] and boronic acids[3b,3f-g] are achieved. Pd-catalyzed approaches to functionalization of chromones with arenes have also been reported utilizing excess of Ag salts in strong acids.[3h] Notwithstanding the advances attained, most of the developed approaches require expensive metal catalysts which are sensitive to oxygen and moisture and require the use of more expensive supporting ligands and costly additives. Also, most of TMs are toxic, and removal of trace amounts of their impurities from final products, especially in pharmaceutical industry, is costly and challenging. These difficulties have prompted chemists to employ alternative pathways to construct C–C bonds under TM-free conditions. This field has attracted increasing attention in recent years and a plethora of reactions released have now been conducted under these conditions.[4]

As part of our continuing interest in functionalization of heterocycles,[5] and to establish a complementary route for construction of flavone-based prominent lead compounds, we envisioned TM-free arylation of chromone-2-carboxylic acids with arylboronic acids. While a direct arylation of chromones towards flavones excluding metals remains elusive, it would be one of the greenest and most powerful procedures for quick synthesis of a large library of natural and unnatural flavones. This approach may exhibit interesting features as avoidance of expensive transition-metals, mild conditions and generation of environmentally friendly side products.

We commenced our study using chromone-2-carboxylic aid (**1a**) and p-tolylboronic acid (**2a**) as model substrates to verify our hypothesis. A brief solvent survey in presence of $K_2S_2O_8$ as a



Scheme 1. Biologically interesting natural and synthetic Flavones.

[a] *Nanobiomaterials group, Pharmaceutical Sciences Research Center, Tehran University of Medical Sciences, Tehran 141761411, Iran. E-mail: mkhoobi@tums.ac.ir, Mehdi.khoobi@gmail.com*
[b] *School of Chemistry, College of Science, University of Tehran, P.O. Box 14155-6455, Tehran, Iran. E-mail: jafarpur@khayam.ut.ac.ir*
[c] *Department of Pharmaceutical Biomaterials and Medical Biomaterials Research Center, Faculty of Pharmacy, Tehran University of Medical Sciences, Tehran, Iran.*
[d] *School of Physical Sciences, University of Tasmania, Private Bag 75, Hobart, Tasmania 7001, Australia. E-mail: Alireza.Ariafard@utas.edu.au*
[e] *Department of Chemistry, Faculty of Science, Central Tehran Branch, Islamic Azad University, Shahrak Gharb, Tehran, Iran.*
Electronic Supplementary Information (ESI) available: Experimental procedures and characterization data. See DOI: 10.1039/x0xx00000x

Table 1 Optimization of reaction conditions for arylation of chromone-2-carboxylic acid[a]

Entry	Solvent	Oxidant (equiv)	T (°C)	Yield (%)[b]
1	DMSO	$K_2S_2O_8$ (2.0)	100	15
2	DCE[c]	$K_2S_2O_8$ (2.0)	100	0
3	H_2O	$K_2S_2O_8$ (2.0)	100	68
4	H_2O/DMSO 1:1	$K_2S_2O_8$ (2.0)	100	10
5	H_2O/DCE[c] (1:1)	$K_2S_2O_8$ (2.0)	100	75
6	**H_2O/DCE (4:1)**	**$K_2S_2O_8$ (2.0)**	**100**	**82**
7	H_2O/DCE (8:2)	H_2O_2 (2.0)	100	trace
8	H_2O/DCE (8:2)	BP[d] (2.0)	100	61
9	H_2O/DCE (4:1)	$K_2S_2O_8$ (2.0)	120	81

[a]Reaction conditions: **1a** (0.5 mmol), **2a** (1 equiv), oxidant (2 equiv), solvent (3 mL), 100 °C, 2 h; [b]Isolated yield. [c]DCE = 1,2-Dichloroethane. [d]BP = Benzoyl peroxide.

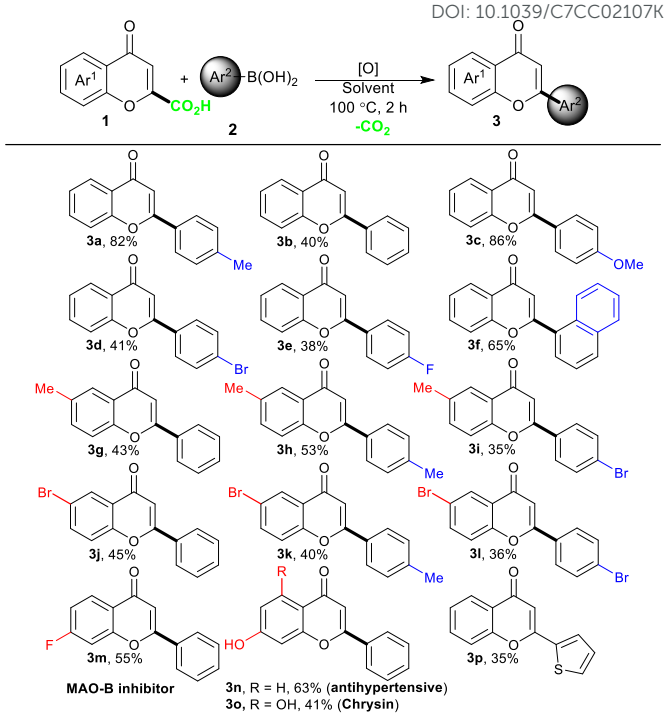
low-priced, commercially available and nontoxic radical initiator, approved H_2O-DCE interface as the most effective one (Table 1, entries 1-5). Importantly, a confident relationship between the solvent volume ratio and the reaction earning was observed where increasing the water content markedly enhanced the yield (entry 6). An increase or decrease in amount of the initiator had no beneficial effect. Moreover, screening the reaction conditions with respect to oxidants proved $K_2S_2O_8$ as the most effective one (entries 7-8). To our delight, under the optimal conditions chromone **1a** participated well in a TM-free arylation/decarboxylation cascade to afford flavone **3a** in 82% yield. This unprecedented protocol may afford a viable alternative route to flavones with an emphasis on avoiding toxic metals and harsh conditions.

Next we sought to explore the scope of the reaction for construction of various structurally diverse flavones employing chromones and arylboronic acids with different electronic and steric circumstances. As it is exposed in Table 2, various phenylboronic acids comprising alkyl, methoxy and halo groups were compatible with this reaction (**3a**-**3e**). Furthermore, sterically demanding naphthylboronic acid with an ortho substitution pattern proved as a suitable coupling partner for arylation of chromone (**3f**). A substrate scope with respect to chromones was considered next where, different alkyl, hydroxyl and halo groups at different positions were well tolerated. It is noteworthy that methyl substitution at different positions of the flavone nucleus retains the potency of the compound as gastroprotective activity (**3g**-**3i**).[6] Bromo-substituted chromone joined the cascade reaction and resulted representative halo substituted flavones (**3j**-**3l**) as good partners for further functionalizations. Flavones with fluoro group at ring A are proved to be selective MAO-B inhibitors which can be easily collected by the present procedure (**3m**).[7a] Gratifyingly, hydroxy-substituted chromone participated well in this arylation process to afford flavone **3n** in 63% yield which can be the drug of interest as novel antihypertensive agent.[8] Satisfyingly, chrysin **3o** with antioxidant activities[1] was also constructed successfully in moderate yield via arylation of 5,7-dihydroxy chromone applying the current protocol. Lastly, thiophene-2-boronic acid participated well in this procedure, to afford heteroarylated chromone **3p** which is confirmed as a selective inhibitor towards MAO-A.[7b]

These results motivated us to expand the scope of this green approach for direct arylation of additional chromenone

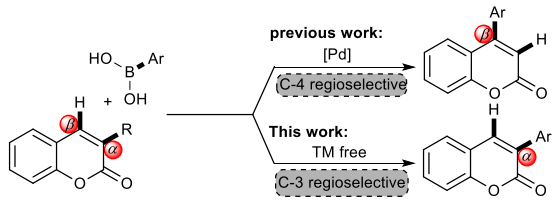
Table 2 Scope of the regioselective arylation of chromones towards flavones[a]

View Article Online DOI: 10.1039/C7CC02107K



[a]All reactions were run under the optimized reaction conditions.

frameworks such as coumarins. The omnipresence of arylcoumarin scaffolds in pharmaceutical and materials sciences[9] ensures a constant demand for their efficient synthesis. Compared to classical strategies, TM-catalyzed approaches for direct instalment of aryls on coumarins are the most prevalent and desired ones conveyed for construction of privileged arylcoumarin scaffolds.[10] Thus far, we also have settled some progresses in TM-catalyzed C-3 arylation of coumarins with arenes,[10e] arylsulfonyl chlorides[10d] and halo arenes[10h] in recent years. Furthermore, we also have conveyed Pd-catalyzed arylation of coumarins by means of arylboronic acids where, the regioselectivity was nonetheless in bias of β–arylation.[3f, 10g] However, when we employed the present methodology for arylation of coumarins avoiding any TMs, a fascinating switch in regioselectivity occurred and aryls were remarkably installed at α-position of the enone ring (Scheme 2). With this interesting outcome, we envisioned expanding the scope of the reaction to include more arylboronic acids as well as coumarins with different electronic natures (Table 3). Coumarin-3-carboxylic acids with either electron-donating or -withdrawing groups furnished the desired products (**5a**-**5r**) in moderate to good yields with exquisite C3-selectivity. Nicely,

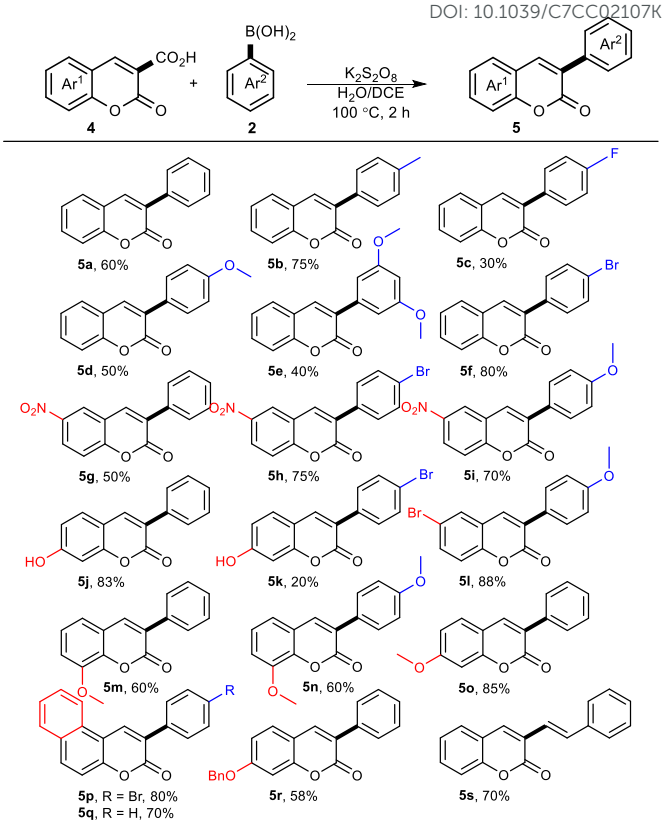


Scheme 2. TM versus TM-free approaches toward arylation of coumarins.

the arylation proceeded reasonably with electron deficient coumarins containing nitro group which are hardly conveyed in TM-catalyzed approaches (**5g**-**5i**). It is noteworthy that the reaction worked very well even with sensitive functionalities such as a hydroxyl group (**5j**-**5k**). The significant feature that eliminates the requirement of protection of hydroxyl groups makes this procedure practicable for preparation of hydroxylated 3-aryl coumarins having diverse biological activities. Bromo-substituted substrates were satisfactorily converted to 3-arylcoumarins in yields exceeding 75% which are synthetically useful intermediates for subsequent modifications (**5f**, **5k**-**5l**). Arylation of benzocoumarins also proceeded smoothly to afford the desired products in high yields (**5p**-**5q**). The reaction also showed perfect efficacy for preparation of styryl coumarin **5s** which are valuable backbones with increased spectroscopic bands intensity.[11]

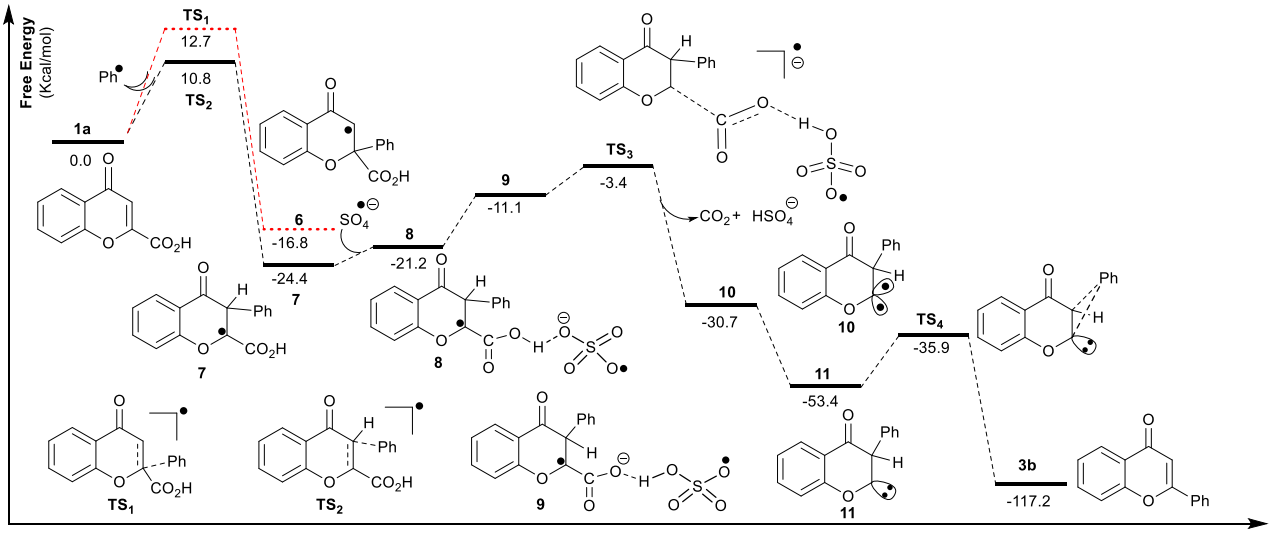
To get insight into the reaction mechanism, a plausible radical reaction track (confirmed by reaction suppression in presence of TEMPO) was explored by DFT calculations (B3LYP/6-31+G (d) method, see SI). First, we investigated on the addition of aryl radical (generated from arylboronic acid through thermal decomposition of peroxydisulfate) on two possible C-2 and C-3 positions of chromone-2-carboxylic acid (Scheme 3). Remarkably, the data showed that transition state related to phenyl radical addition to chromone ring at C-3 (TS_2) has a lower energy than addition to C-2 (TS_1) and later, intermediate **7** remains 7.6 kcal/mol more stable than **6**. Subsequent decarboxylation involves sulfate radical anion (SO_4•–) mediated H-atom abstraction from carboxylic acid intermediate **8**. Next a single electron transfer from sulfate to C-2 occurs followed by decarboxylation via TS_3. This process leaves one electron on C-2 and generates a triplet carbene intermediate **10**, which in turn converts to singlet state 11, and subsequent phenyl group migration from C-3 to C-2 via TS_4 produces flavone **3b**. Based on these results, DFT calculations point to an unprecedented regioselective C-3 arylation of chromone-2-carboxylic acid and subsequent C-3 to C-2 aryl migration mechanism. Similar result was obtained for arylation of coumarins (see SI).

Table 3 Scope of the regioselective arylation of coumarins with aryl boronic acid[a]



[a]All reactions were run under the optimized reaction conditions.

In conclusion, we have described an unprecedented transition-metal-free synthesis of flavones and 3-aryl coumarins in one-pot from readily available chromenones and boronic acids. $K_2S_2O_8$ in an aqueous media proved to be enough to ensue two steps of the reaction cascade in a short reaction time. Providing a practical and green condition, we hope this protocol may find its way as an alternative approach for construction of flavones and aryl coumarins in small and large-scales.



Scheme 3. Free energy (kcal/mol) profiles for the proposed mechanism of TM-free arylation of chromone-2-carboxylic acid. Calculated at the B3LYP/6-31+G (d) basis.

View Article Online
DOI: 10.1039/C7CC02107K

Journal Name

COMMUNICATION

We acknowledge the financial support from the Iran Science Elite Federation (ISEF) and Research Council of Tehran University of Medical Sciences (TUMS) and University of Tehran.

Conflicts of interest

There are no conflicts to declare.

Notes and references

1 (a) E. Middleton Jr., C. Kandaswami and T. C. Theoharides, *Pharmacol. Rev*., 2000, **52**, 673; (b) A. K. Verma and R. Pratap, *Tetrahedron*, 2012, **68**, 8523; (c) M. Singh, M. Kaur and O. Silakari, *Eur. J. Med. Chem*., 2014, **84**, 206.

2 For some selected examples see: (a) X. Zhao, J. Zhou, S. Lin, X. Jin and R. Liu, *Org. Lett*., 2017, **19**, 976; (b) F. Zhu, Z. Wang, Y. Li and X.-F. Wu, *Chem.-A Eur. J*., 2017, **23**, 3276; (c) D. Yang, Z. Wang, X. Wang, H. Sun, Z. Xie, J. Fan, G. Zhang, W. Zhang and Z. Gao, *J. Mol. Catal*., 2017, **426**, 24; (d) S. Baruah, P. P. Kaishap and S. Gogoi, *Chem. Commun.*, 2016, **52**, 13004; (e) J. Yang and N. Yoshikai, *Angew. Chem., Int. Ed*., 2016, **55**, 2870; (f) P. Sun, S. Gao, C. Yang, S. Guo, A. Lin and H. Yao, *Org. Lett*., 2016, **18**, 6464; (g) D. Banerjee, U. Kayal and G. Maiti, *Tetrahedron Lett*., 2016, **57**, 1667; (h) Y.-R. Chen, Y. C. Cho and T.-L. Shih, *Tetrahedron*, 2016, **72**, 2006; (i) T. Yatabe, X. Jin, K. Yamaguchi and N. Mizuno, *Angew. Chem., Int. Ed*., 2015, **54**, 13302; (j) M. Naik, S. G. Tilve and V. P. Kamat, *Tetrahedron Lett*., 2014, **55**, 3340; (k) S. Zhang, C. Wan, Q. Wang, B. Zhang, L. Gao, Z. Zha and Z. Wang, *Eur. J. Org. Chem*., 2013, 2080; (l) D. W. Chuang, M. El-Shazly, D. Balaji, Y. M. Chung, F. R. Chang and Y. C. Wu, *Eur. J. Org. Chem*., 2012, **2012**, 4533; (m) Z. Du, H. Ng, K. Zhang, H. Zeng and J. Wang, *Org. Biomol. Chem*., 2011, **9**, 6930; (n) M. Yoshida, Y. Fujino and T. Doi, *Org. Lett*., 2011, **13**, 4526; (o) Q. Yang and H. Alper, *J. Org. Chem*., 2010, **75**, 948; (p) G. W. Kabalka and A. R. Mereddy, *Tetrahedron Lett*., 2005, **46**, 6315; (q) I. Hirao, M. Yamaguchi and M. Hamada, *Synthesis*, 1984, 1076; (r) N. A. R. Hatam and W. G. Nacy, *Tetrahedron Lett*., 1983, **24**, 4455.

3 (a) H. Choi, M. Min, Q. Peng, D. Kang, R. S. Paton and S. Hong, *Chem. Sci*., 2016, **7**, 3900; (b) Y. Shin, C. Yoo, Y. Moon, Y. Lee and S. Hong, *Chem.-Asian J*., 2015, **10**, 878; (c) T. N. Gowala and J. Pabba, *Tetrahedron Lett*., 2015, **56**, 1801; (d) L. Klier, T. Bresser, T. A. Nigst, K. Karaghiosoff and P. Knochel, *J. Am. Chem. Soc.*, 2012, **134**, 13584; (e) S. Messaoudi, J.-D. Brion and M. Alami, *Org. Lett*., 2012, **14**, 1496; (f) M. Khoobi, M. Alipour, S. Zarei, F. Jafarpour and A. Shafiee, *Chem. Commun*., 2012, **48**, 2985; (g) D. Kim, K. Ham and S. Hong, *Org. Biomol. Chem*., 2012, **10**, 7305; (h) K. H. Kim, H. S. Lee, S. H. Kim and J. N. Kim, *Tetrahedron Lett.*, 2012, **53**, 2761; (i) G. A. Kraus and V. Gupta, *Org. Lett*., 2010, **12**, 5278.

4 For reviews on TM-free C−H functionalization see: (a) X. F. Wu, J. L. Gong and X. Qi, *Org. Biomol. Chem.*, 2014, **12**, 5807; (b) C.-L. Sun and Z.-J. Shi, *Chem. Rev.*, 2014, **114**, 9219; (c) S. Roscales and A. G. Csákÿ, *Chem. Soc. Rev.*, 2014, **43**, 8215; (d) T. L. Chan, Y. Wu, P. Y. Choy and F. Y. Kwong, *Chem.-Eur. J.*, 2013, **19**, 15802; (e) C.-L. Sun, Y.-F. Gu, B. Wang and Z.-J. Shi, *Chem.-Eur. J.*, 2011, **17**, 10844; (f) S. Yanagisawa and K. Itami, *ChemCatChem*., 2011, **3**, 827; (g) C.-L. Sun, H. Li, D.-G. Yu, M. Yu, X. Zhou, X.-Y. Lu, K. Huang, S.-F. Zheng, B.-J. Li and Z.-J. Shi, *Nat. Chem*., 2010, **2**, 1044; (h) R. A. Rossi, A. B. Pierini and A. B. Penenory, *Chem. Rev*., 2003, **103**, 71.

5 (a) F. Jafarpour and M. Shamsianpour, *RSC Adv*., 2016, **6**, 103567; (b) F. Jafarpour and M. Abbasnia, *J. Org. Chem*., 2016, **81**, 11982; (c) M. Khoobi, F. Molaverdi, F. Jafarpour, M. Abbasnia, M. Kubicki and A. Shafiee, *Chem. Commun*., 2015, **51**, 11713; (d) F. Jafarpour, N. Jalalimanesh, M. Teimouri and M. Shamsianpour, *Chem. Commun*., 2015, **51**, 225; (e) F. Jafarpour, S. Rahiminejadan and H. Hazrati, *J. Org. Chem.*, 2010, **75**, 3109; (f) F. Jafarpour and H. Hazrati. *Adv. Synth. Catal.*, 2010, **352**, 363.

6 T. H. Babu, K. Manjulatha, G. S. Kumar, A. Hymavathi, A. K. Tiwari, M. Purohit, J. M. Rao and K. S. Babu, *Bioorg. Med. Chem. Lett*., 2010, **20**, 117.

7 (a) F. Chimenti, R. Fioravanti, A. Bolasco, P. Chimenti, D. Secci, F. Rossi, M. Yanez, F. Orallo, F. Ortuso, S. Alcaro, R. Cirilli, R. Ferretti and M. L. Sanna, *Bioorg. Med. Chem*., 2010, **18**, 1273; (b) B. V. Nayak, S. Ciftci-Yabanoglu, S. Bhakat, A. K. Timiri, B. N. Sinha, G. Ucar, M. E. S. Soliman and V. Jayaprakash, *Bioorg. Chem*., 2015, **58**, 72.

8 H. Adcock, *Pharm. J*., 2002, **269**, 599.

9 (a) M. A. Musa, M. Y. Joseph, L. M. Latinwo, V. Badisa and J. S. Cooperwood, *Anticancer Res*., 2015, **35**, 653; (b) M. A. Musa, L. M. Latinwo, C. Virgile, V. L. D. Badisa and A. J. Gbadebo, *Bioorg. Chem*., 2015, **58**, 96; (c) M. J. Matos, F. Rodriguez-Enriquez, S. Vilar, L. Santana, E. Uriarte, G. Hripcsak, M. Estrada, M. I. Rodriguez-Franco and D. Vina, *Bioorg. Med. Chem. Lett*., 2015, **25**, 642 and references cited therein; (d) Z.-S. Wang, Y. Cui, K. Hara, Y. Dan-oh, C. Kasada and A. Shinpo, *Adv. Mater*., 2007, **19**, 1138; (e) S. A. Swanson, G. M. Wallraff, J. P. Chen, W. J. Zhang, L. D. Bozano, K. R. Carter, J. R. Salem, R. Villa and J. C. Scott, *Chem. Mater*., 2003, **15**, 2305; (f) H. J. Kim, J. E. Park, M. G. Choi, S. Ahn and S. K. Chang, *Dyes Pigm*., 2010, **84**, 54.

10 (a) J.-W. Yuan, L.-R. Yang, Q.-Y. Yin, P. Mao and L.-B. Qu, *RSC Adv*., 2016, **6**, 35936; (b) Z. She, Y. Shi, Y. Huang, Y. Cheng, F. Song and J. You, *Chem. Commun*., 2014, **50**, 13914; (c) S. Paul, K. Pradhan, S. D. Ghosh and A. R. Das, *Adv. Synth. Catal*., 2014, **356**, 1301; (d) F. Jafarpour, M. B. A. Olia and H. Hazrati, *Adv. Synth. Catal*., 2013, **355**, 3407; (e) F. Jafarpour, H. Hazrati, N. Mohasselyazdi, M. Khoobi and A. Shafiee, *Chem. Commun.*, 2013, **49**, 10935; (f) F. Jafarpour, S. Zarei, M. B. A. Olia, N. Jalalimanesh and S. Rahiminejadan, *J. Org. Chem*., 2013, **78**, 2957; (g) M. Khoobi , F. Molaverdi , M. Alipour , F. Jafarpour , A. Foroumadi and A. Shafiee; *Tetrahedron*, 2013, **69**, 11164; (h) S. Messaoudi, J.-D. Brion and M. Alami, *Org. Lett*., 2012, **14**, 1496; (i) M. Min and S. Hong, *Chem. Commun*., 2012, **48**, 9613; (j) M. J. Matos, S. Vazquez-Rodriguez, F. Borges, L. Santana and E. Uriarte, *Tetrahedron Lett*., 2011, **52**, 1225; (k) K. Welser, J. Grilj, E. Vauthey, J. W. Aylott and W. C. Chan, *Chem. Commun*., 2009, 671; (l) M. Mosrin, G. Monzon, T. Bresser and P. Knochel, *Chem. Commun*., 2009, **37**, 5615; (m) M. S. Schiedel, C. A. Briehn and P. Bauerle, *Angew. Chem., Int. Ed*., 2001, **40**, 4677.

11 X. Wang, S.-Y. Li, Y.-M. Pan, H.-S. Wang, Z.-F. Chen and K.-B. Huang, *J. Org. Chem*., 2015, **80**, 2407.