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Oxidative Route to Pyrroloisoquinoline-2,3-dione

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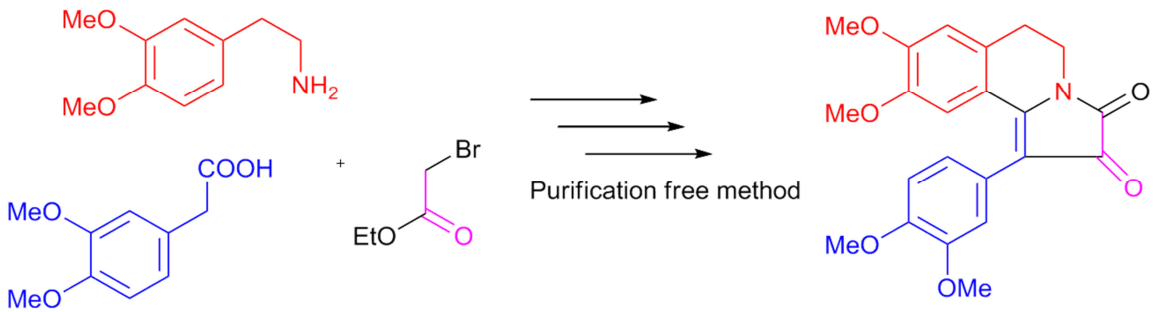
Abstract

We herein report an efficient constructive method for synthesis of structurally important Pyrroloisoquinoline-2,3-dione from dihydroisoquinoline through oxidative cyclisation. Process is optimised to give best efficiency at gram scale and laborious purification techniques such as column chromatography or recrystallisation were avoided in all steps further featuring uniqueness of this method as compared to the available literature.



Dihydropyrrolo[2,1-*a*]isoquinoline-2,3-dione

Keywords: Isoquinoline, pyrrole, aerobic oxidation, synthesis, green chemistry, dione

Introduction

Multiannular heterocycles are frequently encountered in several anticancer, antiviral, antibacterial compounds and naturally occurring microbial or marine metabolites or phytochemicals.[1-4]

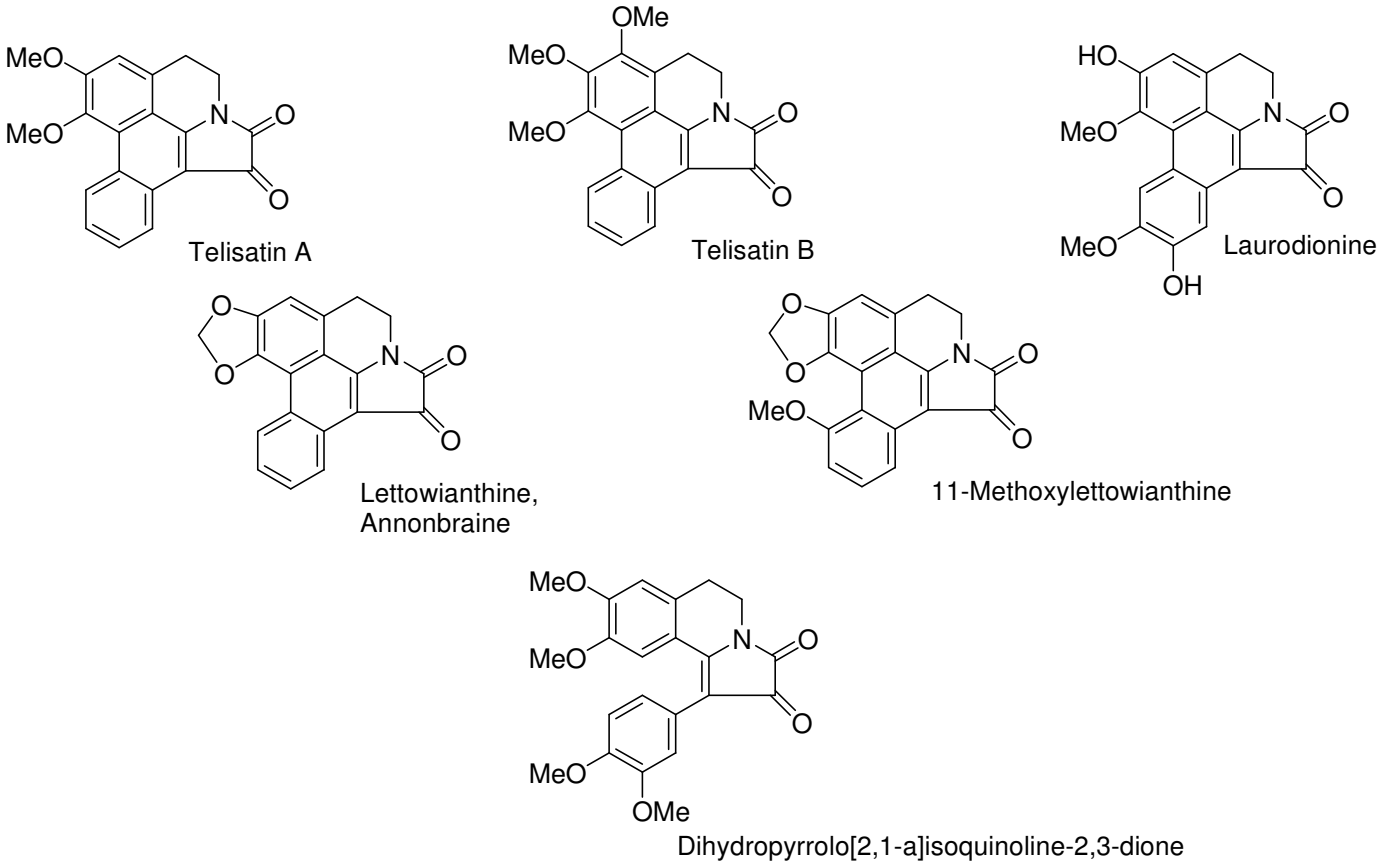


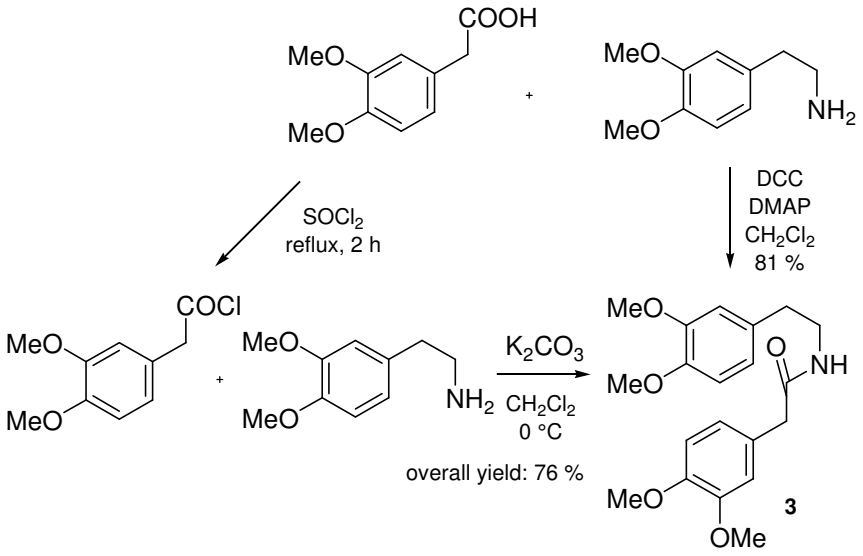
Figure 1. Naturally occurring pyrroloquinoline-1,2-diones and pyrroloisoquinoline-2,3-dione under study.

Pyrroloquinoline-1,2-diones[5-13] are observed in natural compounds such as telisatin A and B, laurodionine, annonbraine, methoxylettowianthine as depicted in Figure 1.

During our studies towards medicinally important organic heterocycles,[14-16] we encountered a route for synthesis of Pyrroloisoquinoline-2,3-dione[17-19] which are structurally similar to pyrroloquinoline-1,2-diones. In this paper we describe an efficient, gram scale, purification free method for synthesis of pyrroloisoquinoline-2,3-dione **1** from dihydroisoquinoline **2** through oxidative cyclisation.

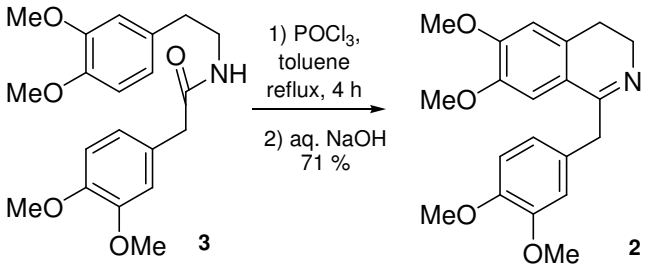
Results and Discussion

We began by preparing secondary amide **3** of homoveratric acid and homoveratryl amine by two alternate methods[20] via acid chloride and via DCC coupling as described in scheme 1.

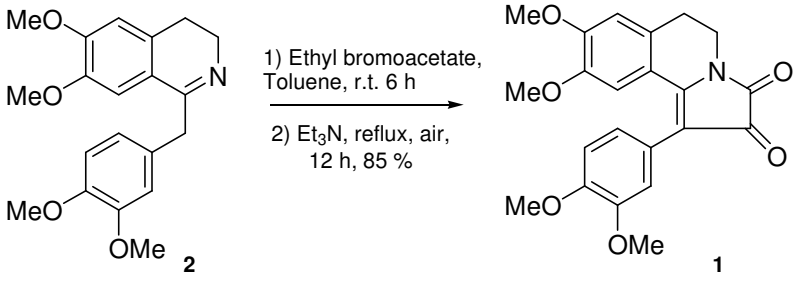


Scheme 1. Synthesis of secondary amide 3.

Dihydroisoquinoline **2** was prepared by Bischler-Napieralski reaction[20-25] (Scheme 2) on amide **3**. Ethyl bromoacetate with dihydroisoquinoline **2** gave the corresponding salt which was *in situ* treated with triethylamine in aerobic refluxing condition. The overall product obtained was identified to be pyrroloisoquinoline-2,3-dione **1**. With process optimisation to give best efficiency, (Scheme 3) laborious purification techniques such as column chromatography or recrystallisation were avoided in all steps further featuring uniqueness of this method as compared to the available literature.



Scheme 2. Preparation of dihydroisoquinoline **2**.

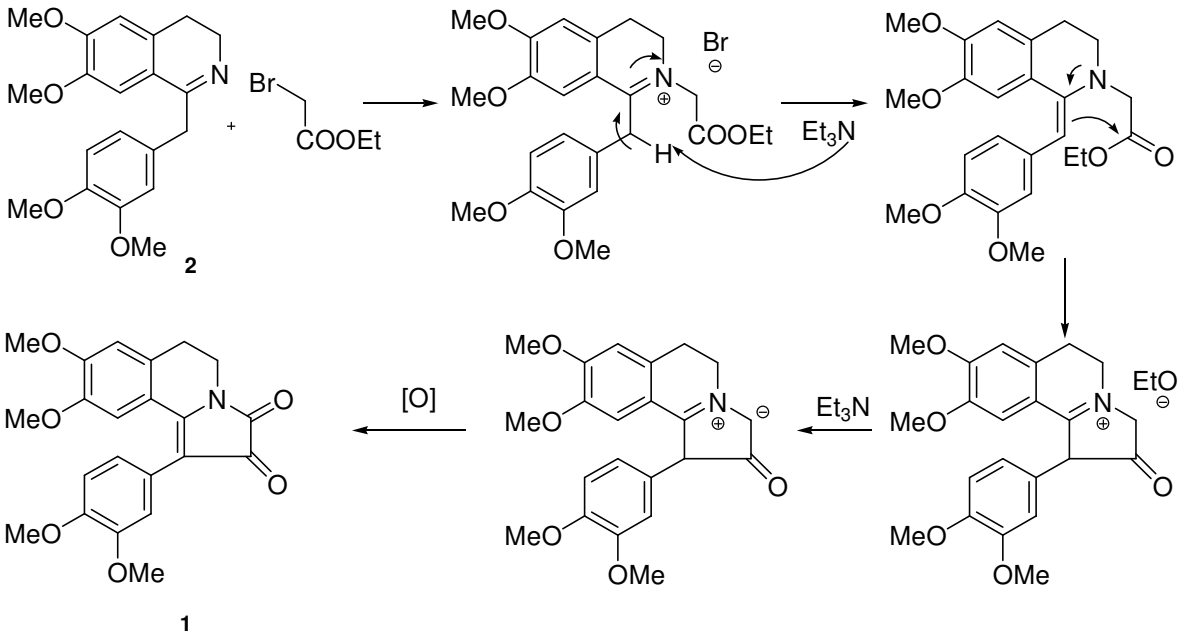


Scheme 3. Preparation of pyrroloisoquinoline-2,3-dione **1**.

On successful method development, we also propose herein a probable mechanistic pathway as described in scheme 4 for this constructive transformation. Dihydroisoquinoline **2** reacts with ethyl bromoacetate to

form the quaternary ammonium salt. Addition of base gives enamine ester which undergoes intramolecular cyclisation to give pyrroloisoquinoline.

Further presence of base gives azomethine which undergoes aerobic oxidation to directly give pyrroloisoquinoline-2,3-dione **1**.



Scheme 4. Probable mechanism for transformation of dihydroisoquinoline to pyrroloisoquinoline-2,3-dione.

Conclusions

In conclusion, we have developed an efficient constructive method for synthesis of structurally important Pyrroloisoquinoline-2,3-dione from dihydroisoquinoline through oxidative cyclisation at gram scale. Laborious purification techniques such as column chromatography or recrystallisation were avoided in all steps further featuring uniqueness of this method.

Experimental Section

General. Reagents were purchased from Sigma-Aldrich and were used without further purification. IR spectra were recorded with Shimadzu FTIR instrument. ^{1}H &^{13}C NMR spectra were recorded in DMSO-d_6 with Bruker AVANCE 400 MHz NMR Spectrometer. LCMS were recorded with Shimadzu LCMS instrument. HRMS were recorded with a MicroMass ESQTOF.

***N*-(*3,4*-Dimethoxyphenethyl)-*2*-(*3,4*-dimethoxyphenyl)acetamide (3).** (a) $SOCl_2$ method: Homoveratric acid (5 g, 25.5 mmol) was added to freshly distilled thionyl chloride (15 mL) and refluxed at 100 °C for 3 h. Excess thionyl chloride was removed from reaction mixture by distillation and dry $CHCl_3$ (10 mL) was added. This solution of acid chloride was added dropwise with stirring to an ice cold solution of homoveratryl amine (4.16 g, 23.0 mmol) and K_2CO_3 (5.53 g 40 mmol) in dry $CHCl_3$ (20 mL). This mixture was stirred for 12 h from 0 °C to

r.t. Solvent was removed under vacuum and distilled water (50 mL) was added. The solid thus obtained was filtered and washed with water (20 mL X 3) and dried under vacuum. Analytically pure product **3** was obtained as white amorphous solid in 76% (6.28 g) yield without any further purification. White amorphous solid, mp: 124-125 °C. [lit. mp 124-125 °C][20] IR (KBr): ν_{max} 3325, 2960, 1641, 1589, 1517, 1028 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.60 (t, *J* 6.8 Hz, 2H), 3.36 (m, 2H), 3.41 (s, 2H), 3.75 (s, 3H), 3.76 (s, 3H), 3.79 (s, 3H), 3.81 (s, 3H), 5.37 (br s, 1H), 6.45 (dd, J 8.4, 1.6 Hz, 1H), 6.54 (d, J 1.6 Hz, 1H), 6.62 (m, 3H), 6.73 (m, 1H) ppm. ^{13}C NMR & DEPT (100 MHz, $CDCl_3$): δ 34.97 (CH_2), 40.71 (CH_2), 43.42 (CH_2), 55.81 (CH_3), 55.84 (2x CH_3), 55.89 (CH_3), 111.08 (CH), 111.39 (CH), 111.64 (CH), 112.36 (CH), 120.56 (CH), 121.59 (CH), 127.14 (Cq), 131.00 (Cq), 147.61 (Cq), 148.27 (Cq), 148.91 (Cq), 149.22 (Cq), 171.30 (Cq) ppm.

(b) DCC coupling method: Homoveratric acid (5 g, 25.5 mmol), homoveratryl amine (4.62 g, 25.5 mmol) and DMAP (0.05 g) were added in dry CH_2Cl_2 (25 mL) and cooled to 0 °C. To this mixture, DCC (6.19 g, 30 mmol) was added and stirred from 0 °C to r.t. for 24 h. Water (1 mL) and dioxane (2 mL) was added to this and stirred for 2 h. Solvent was removed under vacuum, CH_2Cl_2 (25 mL) was added, cooled to 0 °C and filtered. The filtrate was again cooled to 0 °C and filtered. The solvent was removed under vacuum and product **3** was obtained as white solid in 81% (7.41 g) yield without any further purification.

***1*-(*3,4*-Dimethoxybenzyl)-*6,7*-dimethoxy-*3,4*-dihydroisoquinoline (2).** Amide **3** (7.18 g, 20 mmol) was dissolved in dry toluene (10 mL) and freshly distilled $POCl_3$ (5 mL) was added slowly and refluxed for 4 h. The reaction mixture was then poured in ice and basified by cooled aq. NaOH solution (10 N) until pH 14. Dihydroisoquinoline **2** was then extracted in CH_2Cl_2 (20 mL X 2), dried by passing through anhy. Na_2SO_4 and concentrated under vacuum to give 71% (4.84 g) yield without any further purification. Viscous oil.[20] ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.89 (m, 2H), 2.76 (t, J 8.0 Hz, 2H), 3.74 (s, 3H), 3.76 (s, 3H), 3.79 (s, 3H), 3.86 (s, 3H), 4.20 (s, 2H), 6.64 (s, 1H), 6.69 (d, J 8.4 Hz, 1H), 6.78 (m, 1H), 6.95 (s, 1H) , 7.09 (s, 1H) ppm. ^{13}C NMR & DEPT (100 MHz, $CDCl_3$): δ 24.95 (CH_2), 33.20 (CH_2), 49.11 (CH_2), 55.89 (CH_3), 56.04 (CH_3), 56.05 (CH_3), 56.12 (CH_3), 110.02 (CH), 112.20 (CH), 112.04 (CH), 121.16 (CH), 126.64 (CH), 131.09 (Cq), 133.89 (Cq), 147.66 (Cq), 149.68 (Cq), 151.71 (Cq), 154.19 (Cq), 156.13 (Cq), 164.69 (Cq) ppm.

***1*-(*3,4*-Dimethoxyphenyl)-*8,9*-dimethoxy-*5,6*-dihydropyrrolo[*2,1-a*]isoquinoline-*2,3*-dione (1)**.

Dihydroisoquinoline **2** (1.1 g, 3.22 mmol) in dry toluene (25 mL) was cooled to 0 °C and Ethyl bromoacetate (0.6 g, 3.4 mmol) in dry toluene (5 mL) was added and stirred from 0 °C to r.t. for 6 h. Further mixture was cooled to 0 °C and insoluble salt was isolated by decanting. To this salt, triethylamine (10 mL) was added and refluxed in air for 12 h. Finally excess triethylamine was removed under vacuum and ice cold distilled water (50 mL) was added. The solid product thus obtained was filtered and washed with water (20 mL X 3) and dried under vacuum. Analytically pure pyrroloisoquinoline **1** was obtained as wine red solid in 85 % (1.08 g) yield without any further purification. Wine red solid, mp: 176-178 °C, IR (KBr): ν_{max} 3021, 1728, 1705, 1624, 1445 cm^{-1}. ^{1}H NMR (400 MHz, DMSO-d_6): δ 3.06 (t, *J* 6.0 Hz, 2H), 3.25 (s, 3H), 3.68 (s, 3H), 3.70 (t, *J* 6.4 Hz, 2H), 3.77 (s, 3H), 3.86 (s, 3H), 6.83 (m, 1H), 6.85 (s, 1H), 6.92 (s, 1H), 7.03 (d, *J* = 8.4 Hz, 1H), 7.09 (s, 1H) ppm. ^{13}C NMR (100 MHz, DMSO-d_6): δ 27.55 (CH_2), 35.90 (CH_2), 54.62 (CH_3), 55.53 (CH_3), 55.61 (CH_3), 55.94 (CH_3), 107.24 (Cq), 111.45 (CH), 112.02 (CH), 112.16 (CH), 113.49 (CH), 115.97 (Cq), 122.56 (CH), 122.94 (Cq), 133.84 (Cq), 146.98 (Cq), 148.37 (Cq), 148.82 (Cq), 153.14 (Cq), 157.05 (Cq), 158.00 (Cq), 182.85 (Cq) ppm. LCMS (*m/z*): $[M+H]^+$ 395.9. HRMS (*m/z)*: calculated for $C_{22}H_{21}NO_6Na$ $[M+Na]^+$: 418.1267; found : 418.1289.

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Supplementary Material

Supplementary data (^{1}H NMR, ^{13}C NMR and DEPT spectra of all the products) associated with this article can be found, in the online version.

References

1. Liu, B.; Jian, L.; Chen, G.; Song, X.; Han, C.; Wang, J. *Chemistry of Natural Compounds* **2014**, *49*, 1172. https://doi.org/10.1007/s10600-014-0855-6
2. Polygalova, N. N.; Mikhailovskii, A. G.; Vikhareva, E. V.; Vakhrin, M. I. *Chemistry of Heterocyclic Compounds* **2007**, *43*, 900. https://doi.org/10.1007/s10593-007-0142-6
3. Hwang, T. L.; Wu, Y. C.; Yeh, S. H.; Kuo, R. Y., *Biochemical Pharmacology* **2004**, *69*, 65. https://doi.org/10.1016/j.bcp.2004.09.010
4. Wu, C.-C.; Wang, W.-Y.; Kuo, R.-Y.; Chang, F.-R.; Wu, Y.-C. *Eur. J. Pharmacology* **2004**, *483*, 187. https://doi.org/10.1016/j.ejphar.2003.10.046
5. Chang, F.-R.; Chen, C.-Y.; Hsieh, T.-J.; Cho, C.-P.; Wu, Y.-C. *J. Chin. Chemical Soc*. (Taipei) **2000**, *47*, 913. https://doi.org/10.1002/jccs.200000124
6. Yang, Y.-L.; Chang, F.-R.; Wu, Y.-C. *Helv. Chim. Acta.* **2004**, *87*, 1392. https://doi.org/10.1002/hlca.200490127
7. Nkunya, M. H. H.; Jonker, S. A.; Makangara, J. J.; Waibel, R.; Achenbach, H. *Phytochemistry* **2000**, *53*, 1067. https://doi.org/10.1016/S0031-9422(00)00012-1
8. Chen, C.-C.; Huang, Y.-L.; Lee, S.-S.; Ou, J.-C. *J. Nat. Prod.* **1997**, *60*, 826. https://doi.org/10.1021/np970147c
9. Menachery, M. D.; Blake, G. W.; Gourley, R. C.; Freyer, A. *J. Nat. Prod*. **1995**, *58*, 1945. https://doi.org/10.1021/np50126a025
10. Saa, C.; Guitian, E.; Castedo, L.; Suau, R.; Saa, J. M. *J Org. Chem*. **1986**, *51*, 2781. https://doi.org/10.1021/jo00364a030
11. Castedo, L.; Saa, C.; Saa, J., M.; Suau, R. *J Org. Chem*. **1982**, *47*, 513. https://doi.org/10.1021/jo00342a028
12. Omar, H.; Mohd. Hashim, N.; Zajmi, A.; Nordin, N.; Abdelwahab, S. I.; Azizan, A. H. S.; Hadi, A. H. A.; Mohd Ali, H. *Molecules* **2013**, *18*, 8994. https://doi.org/10.3390/molecules18088994
13. Dhineshkumar, J.; Lamani, M.; Alagiri, K.; Prabhu, K. R. *Org. Lett*. **2013**, *15*, 1092. https://doi.org/10.1021/ol4001153
14. Kadam, H. K.; Tilve, S. G. *Arkivoc* **2015** (*vi*) 524. http://dx.doi.org/10.3998/ark.5550190.p009.316

15. Kadam, H. K.; Tilve, S. G. *J. Heterocyclic Chem*. **2016**, *53*, 2066. https://doi.org/10.1002/jhet.2213
16. Kadam, H. K.; Malik, D.; Salgaonkar, L.; Mandrekar, K.; Tilve, S. G. *Synth. Commun.* **2017**, *47*, 1980. https://doi.org/10.1080/00397911.2017.1359303
17. Nimgirawath, S.; Udomputtimekakul, P. *Molecules* **2009**, *14*, 917. https://doi.org/10.3390/molecules14030917
18. Thasana, N.; Bjerke-Kroll, B.; Ruchirawat, S. *Synlett* **2008** , *4*, 505. https://doi.org/10.1055/s-2008-1042764
19. Kuo, R.Y.; Wu, C.C.; Chang, F.R.; Yeh, J.L.; Chen, I.J.; Wu, Y.C. *Bioorg. Med. Chem. Lett*. **2003**, *13*, 821. https://doi.org/10.1016/S0960-894X(03)00003-9
20. Szawkalo, J.; Czarnocki, Z., *Monat.Chem.* **2005**, *136*, 1619. https://doi.org/10.1007/s00706-005-0341-8
21. Wu, J.; Talwar, D.; Johnston, S.; Yan, M.; Xiao, J. *Angew. Chem. Int. Ed*. **2013**, *52*, 6983. https://doi.org/10.1002/anie.201300292
22. Makhey, D.; Gatto, B.; Yu, C.; Liu, A.; Liu, L. F.; LaVoie, E. J. *Bioorg. Med. Chem*. **1996**, *4*, 781. https://doi.org/10.1016/0968-0896(96)00054-5
23. Jacobs, J.; Tuyen, N.; Markusse, P.; Stevens, C. V.; Maat, L.; Kimpe, N. *Tetrahedron* **2009**, *65*, 1188. https://doi.org/10.1016/j.tet.2008.11.077
24. Castedo, L.; Iglesias, T.; Puga, A.; Saa, J. M.; Suau, R. *Heterocycles* **1981**, *15*, 915. https://doi.org/10.3987/S-1981-02-0915
25. Saa, J. M.; Cava, M. P. *J Org. Chem*. **1978**, *43*, 1096. https://doi.org/10.1021/jo00400a016

