Facile Synthesis of Emodin Derivatives as Potential MMPIs

Xing-po Wang and Wen-fang Xu*

*The School of Pharmacy, Shandong University, Jinan 250012, P. R. China. *E-mail: xpw6@sdu.edu.cn*

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Emodin (1,3,8-trihydroxy-6-methylanthraquinone) is a major active component of the traditional Chinese medicine -*genus Rhamnus herb* (Dahuang in Chinese). It has been reported that emodin possess many important biological properties, including anticancer, antibacterial and diuretic activities.[1,2] On the other hand, the matrix metalloproteinases (MMPs), a family of zinc dependent proteinases involved in the process of tumor growth, invasion and metastasis, etc, are frequently over expressed by malignant tumors. Among which, gelatinase (MMP-2 and MMP-9) are proved more essential with tumor.[3] Emodin can greatly reduced the overexpression of gelatinase in various tumor lines, such as breast, cervical, prostate, glioma.[4] Thus, emodin derivatives can serve as potential MMP inhibitors (MMPIs). As a part of our efforts to continually develop potential MMPIs,[5] we have prepared a series of emodin derivatives and reported in this paper.

Starting from emodin (1,3,8-trihydroxy-6-methylanthraquinone), the key intermediate (**2**) was accomplished according to the literature.[6] Because the 1,8-hydroxy groups of emodin are adjacent to the 9-carbonyl group forming two intramolecular hydrogen bonds while the 3-hydroxy group is far from 9-and 10-carbonyl group, its reaction activity is more active than the 1-and 8-hydroxy groups. When the emodin reacted with one equivalent of potassium hydroxide in the presence of excess epichlorohydrin, the nucleophilic substituted reaction of 3-hydroxy group with epichlorohydrin was proceeded easily at refluxing temperature. The target product epoxide **2** was obtained as yellow needle crystals, with a little by-product 1,8-dihydroxy-3-(3-chloro-2-hydroxypropoxy)-6-methyl-9,10-anthraquinone (**3**) (Scheme 1).

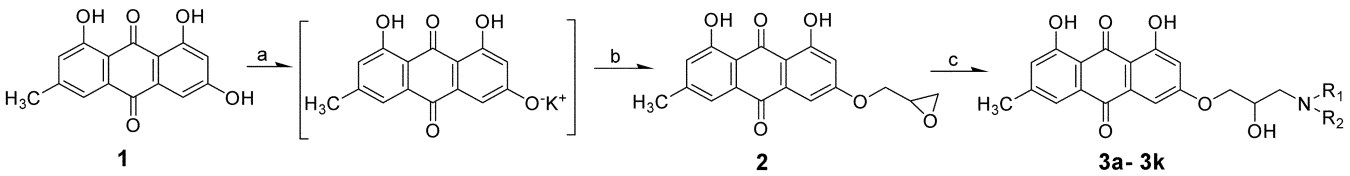
Different from the literature, epichlorohydrin was used both the reactant and the solvent in order to prevent more by-products and force the reaction completely.

Ring opening reaction of epoxide **2** with different amines afforded series of 1,8-dihydroxy-3-(3-substitutedamino-2-hydroxy-propoxy)-6-methyl-9,10-anthraquinones. The reaction is proceeded according to SN_2 mechanism, due to the steric hindrance of position **a**, the nucleophilic amines are inclined to attack position **b** (Scheme 2) to give final product. Besides, different amines need different reaction conditions. The results indicated that when secondary amines were used, the reaction required more high temperature due to their steric hindrance, when the primary amines were used, lower temperature was needed to prevent the side reaction.

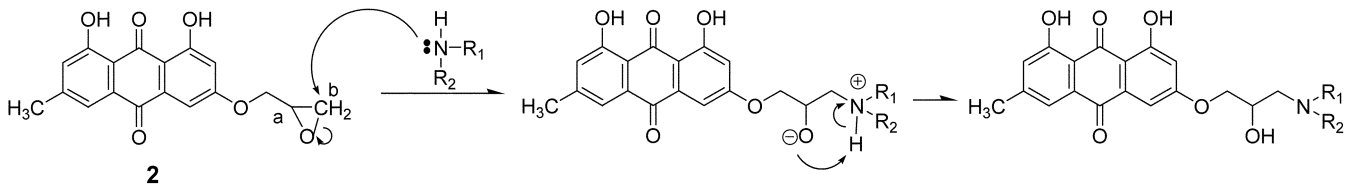
The synthetic route is summarized in Scheme 1 and the results are tabulated in Table 1.

All of the compounds were tested for their antitumor activities against KLE cell line by MTT assay and the result was showed in Table 1. The result suggested that most compounds have different antitumor activity against KLE cell line, a further investigation was underway.

In conclusion, given the availability of emodin and amines, 11 novel emodin derivatives as potential MMPIs were synthesized .

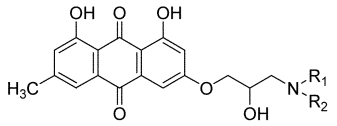


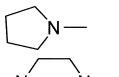
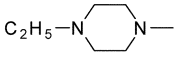
Scheme 1. a) KOH, b) epichlorohydrin, c) HNR_1R_2, $CHCl_3$ or EtOH.



Scheme 2. The mechanism of ring opening reaction.

Table 1. Preparation of emodin derivatives (**3a-3k**)



Entry	R_1-N(R_2)-	Mp (°C)	Isolated Yield (%)	IC_{50} (μg/mL)
3a	CH_3-N(CH_3)-	159-161	56	57.4
3b	$CH_3CH(CH_3)$-NH-	177-179	72	50.2
3c	$(CH_3)_3CH$-NH-	172-174	63	48.0
3d		118-119	79	56.3
3e		117-119	82	44.2
3f	$HOCH_2CH_2NH$-	194-195	73	55.5
3g	*p*-CH_3-C_6H_4NH-	224-225	68	47.3
3h	*p*-Cl-C_6H_4NH-	229-231	74	43.1
3i	2,5-$Cl_2C_6H_3NH$-	340-341	69	51.5
3j	*p*-$NO_2C_6H_4NH$-	267-269	67	32.4
3k	*p*-$CF_3C_6H_4NH$-	176-178	75	33.1

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7. ^{1}H NMR, MS data of target compounds (δ ppm in DMSO-d_6): **3a**: 2.31 (s, 6H), 2.43 (s, 3H), 3.38 (m, 2H), 3.91 (m, 1H), 4.09 (dd, *J* = 4.21, 5.98 Hz, 1H), 4.21 (dd, *J* = 3.18, 7.02 Hz, 1H), 4.96 (d,1H, *J* = 10.3), 6.87-7.55 (4H), 11.98 (bs, 2H); MS (m/z): 372 $[M+H]^+$. **3b**: 0.94 (d, *J* = 7.0, 6H), 2.32 (m, 1H), 2.44 (s, 3H), 3.48 (m, 2H), 3.89 (m, 1H), 4.02 (dd, *J* = 4.01, 5.68 Hz, 1H), 4.13 (dd, *J* = 3.14, 7.15 Hz, 1H), 4.87 (d,1H *J* = 10.17), 6.86-7.56 (4H), 12.01 (bs, 2H); MS (m/z): 386 $[M+H]^+$. **3c**: 1.14 (s, 9H, -C-CH_3), 2.43 (s, 3H), 3.40 (m, 2H), 3.87 (m, 1H), 4.00 (dd, *J* = 3.98, 5.75 Hz, 1H), 4.12 (dd, *J* = 3.15, 7.14 Hz, 1H), 4.88 (d, 1H, *J* = 10.17), 6.78-7.51 (s, 4H), 12.10 (bs, 2H); MS (m/z): 400 $[M+H]^+$. **3d**: 1.57 (t, *J* = 7.10, 4H), 2.26 (m, 4H), 2.43 (s, 3H), 3.44 (m, 2H), 3.91 (m, 1H), 4.08 (dd, *J* = 4.22, 5.88 Hz, 1H), 4.24 (dd, *J* = 3.17, 7.12 Hz, 1H), 4.93 (d, 1H *J* = 10.42), 6.81-7.60 (4H, Ar-H), 11.93 (bs, 2H); MS (m/z): 398 $[M+H]^+$. **3e**: 0.95 (t, *J* = 7.02, 6H), 2.25 (q, 2H), 2.34 (m, 4H), 2.39 (m, 2H), 2.44 (s, 3H,), 2.47 (m, 4H), 3.99 (m, 1H), 4.09 (dd, *J* = 4.07, 6.21 Hz, 1H), 4.21 (dd, *J* = 3.24, 7.12 Hz, 1H), 4.95 (d, 1H, *J* = 10.4), 6.85-7.65 (4H, Ar-H), 11.98 (bs, 2H); MS (m/z): 441 $[M+H]^+$. **3f**: 2.43 (s, 3H), 3.12 (m, 6H), 3.61 (t, *J* = 4.25, 1H), 3.94 (m, 1H), 4.10 (dd, *J* = 4.14, 6.35 Hz, 1H,), 4.20 (dd, *J* = 4.09, 7.08 Hz, 1H), 4.23 (m, 1H), 4.93 (d, 1H *J* = 10.2), 6.88-7.55 (4H, Ar-H), 12.01 (bs, 2H); MS (m/z): 388 $[M+H]^+$. **3g**: 2.13 (s, 1H), 2.42 (s, 3H), 3.10 (m, 1H), 3.22 (m, 1H), 4.01 (m, 1H), 4.14 (dd, 1H, *J* = 4.08, 5.92), 4.23 (dd, 1H, *J* = 3.86, 6.32), 5.26 (d, 1H, *J* = 4.12 Hz), 5.34 (t, *J* = 5.44, 1H), 6.55-7.53 (8H, Ar-H), 11.96 (s, 1H), 12.14 (s, 1H); MS (m/z): 434 $[M+H]^+$. **3h**: 2.42 (s, 3H), 3.09 (m, 1H), 3.25 (m, 1H), 4.01 (m, 1H), 4.13 (dd, 1H, *J* = 4.08, 5.92), 4.22 (dd, 1H, *J* = 3.67, 6.32), 5.30 (d, 1H, *J* = 4.02 Hz), 5.83 (t, *J* = 5.44, 1H), 6.64-7.52 (8H, Ar-H), 11.96 (s, 1H), 12.14 (s, 1H); MS (m/z): 454.5 $[M+H]^+$. **3i**: 2.43 (s, 3H), 3.39 (m, 2H), 4.06 (m, 1H), 4.14 (dd, *J* = 3.24, 5.43 Hz, 1H), 4.22 (dd, *J* = 3.45, 6.13 Hz, 1H), 5.47 (m, 1H), 5.60 (d, 1H, *J* = 4.98 Hz), 6.59-7.54 (7H, Ar-H), 12.06 (br, 2H); MS (m/z): 489 $[M+H]^+$. **3j**: 2.43 (s, 3H), 3.10 (m, 1H), 3.24 (m, 1H), 4.03 (m, 1H), 4.13 (dd, 1H, *J* = 4.08, 5.92), 4.21 (dd, 1H, *J* = 3.68, 6.33), 5.31 (d, 1H, *J* = 4.02 Hz), 5.85 (t, *J* = 5.44, 1H), 6.65-7.54 (8H, Ar-H), 11.95 (s, 1H), 12.12 (s, 1H); MS (m/z): 465 $[M+H]^+$. **3k**: 2.44 (s, 3H), 3.32 (m, 1H), 3.60 (m, 1H), 4.05 (m, 1H), 4.17 (dd, 1H, *J* = 4.36, 5.83), 4.24 (dd, 1H, *J* = 4.20, 6.00), 5.25 (d, 1H, *J* = 4.01 Hz), 6.29 (t, *J* = 5.87, 1H), 6.74-7.55 (8H, Ar-H), 12.04 (br, 2H); MS (m/z): 488 $[M+H]^+$.