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AN EFFICIENT APPROACH FOR THE SYNTHESIS OF 2-[(3-CYANO-1-OXO-4-(3, 4, 5-TRIMETHOXYPHENYL)-1, 2, 3, 4-TETRAHYDRONAPHTHALEN-2-YL) THIO] BENZOIC ACID DERIVATIVES

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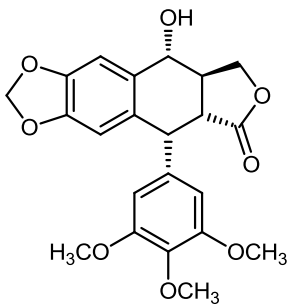
ABSTRACT
A series of 2-[(3-cyano-1-oxo-4-(3, 4, 5-trimethoxyphenyl)-1, 2, 3, 4-tetrahydronaphthalen-2-yl) thio] benzoic acid have been synthesized with a significant stereo selectivity and improved yields in a single step by employing thiosalicylic acid in presence of Tetra-n-butylammonium bromide /methanol solvent system. The structures of the synthesized compounds were confirmed by spectral and elemental analysis data.

KEYWORDS: thiosalicylic acid, tetra-n-butylammonium bromide, dehalogenation.

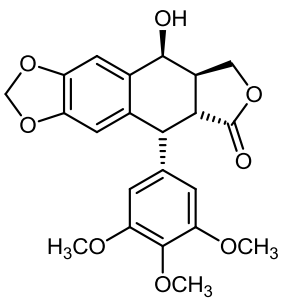
INTRODUCTION

Podophyllotoxin (PPT, 1, Fig. 1), a naturally occurring aryltetralin lignan, holds a unique position among natural products having been known for approximately 1000 years from its first application in folk medicines to its most recent developments in PPT-derived antitumor agents. Interest in PPT was initiated by Kaplan, who demonstrated its curative effect against tumor growth (*Condylomata acuminata*), and subsequently by King and Sullivan, who found its antiproliferative effect to be similar to that of colchicine at the cellular level.[1] But Due to its complicated side effects such as nausea, vomiting, and damage of normal tissues, attempts to use podophyllotoxin in the treatment of human neoplasia have been mostly unsuccessful. The unique cyclolignan scaffold of 1 has however drawn a lot of attention for the discovery and development of new anticancer agents. Extensive structural modifications, particularly at the C-4 and C-4' position of podophyllotoxin have led to the development of many semisynthetic derivatives of podophyllotoxin. Among them, five semisynthetic derivatives, etoposide (2), teniposide (3), etopophos (4), GL-331 (5) and TOP-53 (6) (Figure 1) are currently used in the chemotherapy for a variety of cancers, including small-cell lung cancer, non-Hodgkin's lymphoma, leukemia, Kaposi's sarcoma, neurobslastoma and soft tissue sarcoma.[2-4] Their anticancer activity proceeds through a mechanism of action entirely different from that of their parent compound podophyllotoxin (1). Etoposide (2), teniposide (3), and etopophos (4) are three semisynthetic glucosidic cyclic acetals of 1, and in particular, etoposide (2) is considered to be one of the most successful pharmaceuticals derived from plants. Both GL-331 (5) and TOP-53 (6) are more active than etoposide (2) and are currently under clinical investigation.[5-7]

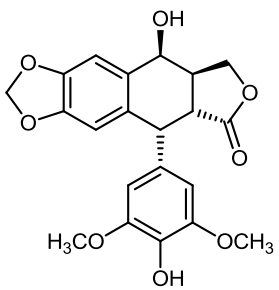
Thus we describe here an efficient approach for the synthesis of 2-[(3-cyano-1-oxo-4-(3, 4, 5-trimethoxyphenyl)-1, 2, 3, 4-tetrahydronaphthalen-2-yl) thio] benzoic acid derivatives as a key structural compound.



Podophyllotoxin 1



epipodophyllotoxin (2)



4-demethylepipodophylltoxin (3)

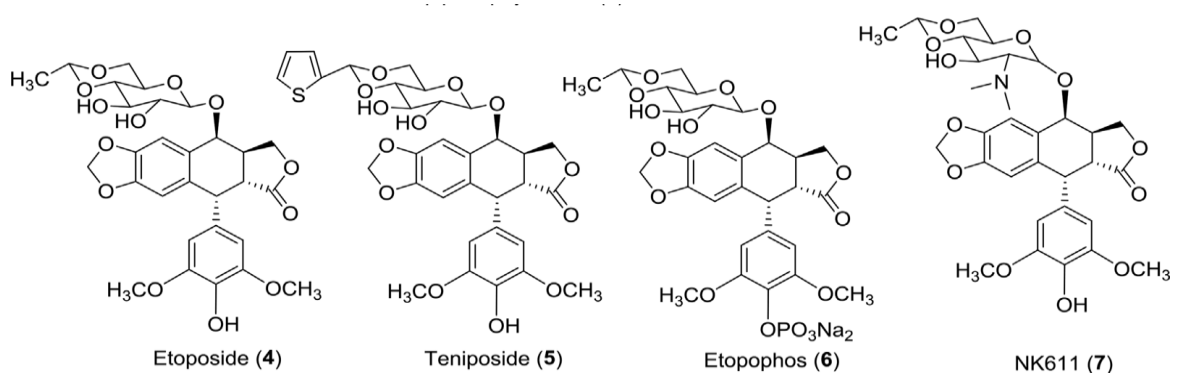
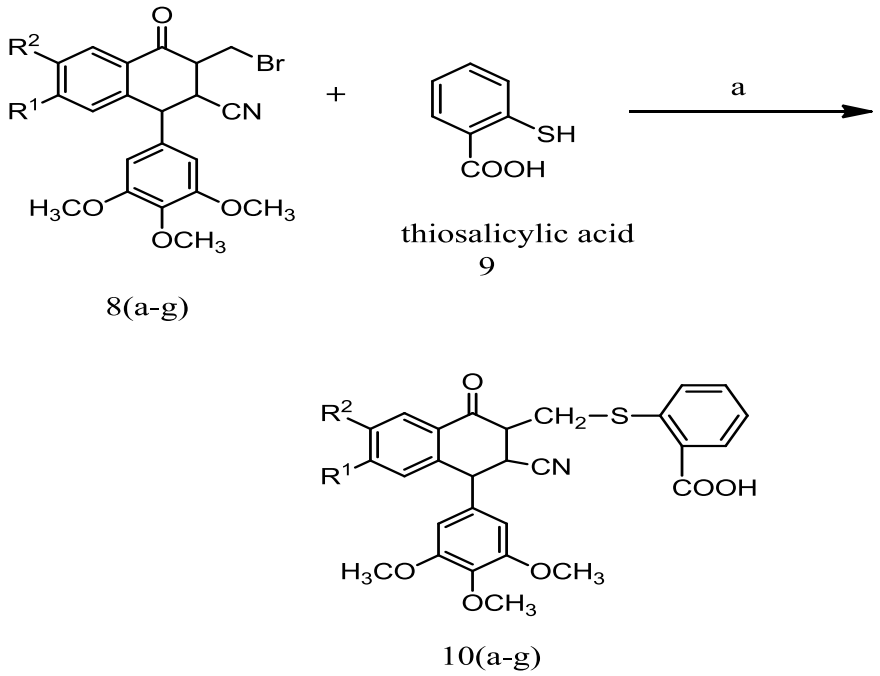


Figure 1; **Structures of podophyllotoxin (1, PPT), epipodophyllotoxin (2, EPPT), 4'-demethylepipodophyllotoxin (3, DEPPT), etoposide (4, ETO), teniposide (5), etopophos (6), NK-611(7),**

RESULTS AND DISCUSSION

Substituted 2-[(3-cyano-1-oxo-4-(3, 4, 5-trimethoxyphenyl)-1, 2, 3, 4-tetrahydronaphthalen-2-yl) thio] benzoic acid 10a-g were prepared from substituted 3-bromomethyl-1-phenyl-1, 2, 3, 4-tetrahydronaphthalene-2-carbonitrile 8a-g (scheme 1) by substitution reaction with thiosalicylic acid using TBAI and potassium carbonate in methanol, stirred for 10 min at 25-28^{0}C under nitrogen gas atmosphere and refluxed for 4-5hours at 65-68^{0}C. After completion of the reaction, the reaction mixture was extracted with water followed by dichloromethane. The aqueous layer was collected and was evaporated to get crude solid which was purified by column chromatography on silica gel using hexane/ethyl acetate (80:20v/v). Their structures were confirmed by spectroscopic evidences.



Scheme 1: reagents and condition: a) TBAI, K_2CO_3, methanol, heat at 65-68^{0}C

Compounds	R_1	R_2	Yield (%)	Colour	M.P (^{0}C)
10a	OCH_3	OCH_3	71.08	white	132-135
10b	H	OH	61.98	white	112-114
10c	H	CH_3	61.78	white	102-105
10d	H	Cl	72.02	white	122-125
10e	H	H	61.58	white	101-103
10f	H	OCH_3	62.08	white	132-135
10g	H	NH_2	61.48	white	125-128

^{1}H-NMR of the compound shows signals of a singlet at δ 11.0 indicating the presence of carboxylic group and a doublet at δ 4.00-4.05 for the proton bonding to cyanide group and sulphur group. ^{13}C-NMR shows signals as singlet at 191.5 ppm pertaining to the carbonyl group, a singlet at 168.1ppm for carboxylic acid and a singlet at 119.2 ppm for cyanide group.

2-((3-cyano-6, 7-dimethoxy-1-oxo-4-(3, 4, 5-trimethoxyphenyl)-1, 2, 3, 4-tetrahydronaphthalen-2-yl) thio) benzoic acid (10a)

^{1}H NMR: 11.01-11.20(1 H, s, COOH), 8.30-8.35(1H, d, Ar-H), 7.69-7.42(4 H, m, Ar-H), 7.07-6.89(s, 1H, Ar-H), 4.01-4.09(3 H, d, CH_2), 3.92(15 H, s, OCH_3), 2.79(2H, d CH_2); ^{13}C NMR: 191.5, 168.1, 154.7, 153.4, 147.2, 142.6, 137.3, 136.7, 134.1, 133.8, 133.2, 127.3, 126.7, 126.5, 125.0, 119.2, 110.5, 109.2, 106.6, 60.8, 56.1, 53.8, 36.6,31.6, 30.0;MS, *m/z*: 563.2 (*M*+). Anal. Calcd. For $C_{30}H_{29}NO_8$ S: C, 63.93; H, 5.19; O, 22.71; S, 5.69; Found: C, 63.94; H, 5.18; O, 22.71; S, 5.68 %.

2-((3-cyano-6-hydroxy-1-oxo-4-(3,4,5-trimethoxyphenyl)-1,2,3,4-tetrahydronaphthalen-2-yl)methyl)thio)benzoic acid (10b)

^{1}H NMR: 11.01-11.20(1 H, s, COOH), 8.30-8.19 (2 H, d, Ar-H), 7.69-7.42(3 H, m, Ar-H), 7.11(1 H, s, Ar-H), 6.89(s, 1H, Ar-H), 4.01-4.09(3 H, d, CH_2), 3.92(9 H, s, OCH_3), 2.79(2H, d CH_2); ^{13}C NMR: 191.5, 161.9, 168.1, 153.4, 142.6, 141.9, 137.3, 136.7, 134.1, 133.2, 130.7, 126.7, 126.6, 126.5, 125.0, 120.6, 113.3, 106.6, 60.8, 56.1, 53.8, 36.6,31.6, 30.0; MS, *m/z*: 519.10 (*M*+). Anal. Calcd. For $C_{28}H_{25}NO_7S$: C, 64.73; H, 4.85; N, 2.70; O, 21.56; S, 6.17; Found: C, 64.72; H, 4. 86; N, 2.72; O, 22.55; S, 6.15%.

2-((3-cyano-6-methyl-1-oxo-4-(3,4,5-trimethoxyphenyl)-1,2,3,4-tetrahydronaphthalen-2-yl)methyl)thio)benzoic acid (10c)

^{1}H NMR: 11.01-11.20(1 H, s, COOH), 8.35-8.30(1H, d, Ar-H), 7.80-7.13(6 H, m, Ar-H), 7.07-6.89(s, 1H, Ar-H), 4.01-4.09(3 H, d, CH_2), 3.92(9 H, s, OCH_3), 2.79(2H, d CH_2), 2.34(3 H, t, CH_3); ^{13}C NMR: 191.5, 168.1, 153.4, 143.3, 142.6, 140.4, 136.7, 134.1, 133.2, 131.0, 128.0, 126.7, 126.4, 125.2, 125.0, 119.2, 106.6, 60.8, 56.1, 53.8, 36.6, 31.6,30.0, 21.6;MS, *m/z*: 517.25 (*M*+). Anal. Calcd. For $C_{29}H_{27}NO_6S$: C, 67.29; H, 5.26; N, 2.71; O, 18.55; S, 6.20; Found: C, 67.29; H, 5.25; N, 2.72; O, 18.57; S, 6.21 %.

2-((6-chloro-3-cyano-1-oxo-4-(3,4,5-trimethoxyphenyl)-1,2,3,4-tetrahydronaphthalen-2-yl)methyl)thio)benzoic acid (10d)

^{1}H NMR: 11.01-11.20(1 H, s, COOH), 8.36-8.35(1H, d, Ar-H), 7.86-7.39(6 H, m, Ar-H), 7.01(s, 1H, Ar-H), 4.01-4.09(3 H, d, CH_2), 3.92(9 H, s, OCH_3), 2.79(2H, d CH_2); ^{13}C NMR: 191.5, 168.1, 153.4, 142.6, 141.9, 139.2, 137.3, 136.7, 134.1, 133.2, 132.1, 130.7, 127.9, 126.7, 126.5, 126.2, 125.0, 119.2, 106.6, 60.8, 56.1, 53.8, 36.6, 31.6, 30.0;MS, *m/z*: 538.15 (*M*+). Anal. Calcd. For $C_{28}H_{24}NClO_6$ S: C, 62.51; H, 4.50; Cl, 6.59; O, 17.84; S, 5.96; Found: C, 62.52; H, 4.51; Cl, 6.56; O, 17.85; S, 5.95 %.

2-((3-cyano-1-oxo-4-(3,4,5-trimethoxyphenyl)-1,2,3,4-tetrahydronaphthalen-2-yl) methyl)thio)benzoic acid (10e)

^{1}H NMR: 11.01-11.20(1 H, s, COOH), 8.30-8.35(1H, d, Ar-H), 7.69-7.42(4 H, m, Ar-H), 7.07-6.89(s, 1H, Ar-H), 4.01-4.09(3 H, d, CH_2), 3.92(9 H, s, OCH_3), 2.79(2H, d CH_2);^{13}C NMR: 191.5, 168.1, 154.7, 153.4, 147.2, 142.6, 137.3, 136.7, 134.1, 133.8, 133.2, 127.3, 126.7, 126.5, 125.0, 119.2, 110.5, 109.2, 106.6, 60.8, 56.1, 53.8, 36.6,31.6, 30.0;MS, *m/z*: 503.12 (*M*+).Anal. Calcd. For $C_{28}H_{25}NO_6S$: C, 66.78; H, 5.00; O, 19.06; S, 6.37; Found: C, 66.77; H, 5.02; O, 19.07; S, 6.38%.

2-((3-cyano-6-methoxy-1-oxo-4-(3,4,5-trimethoxyphenyl)-1,2,3,4-tetrahydronaphthalen-2-yl) methyl)thio)benzoic acid (10f)

^{1}H NMR: 11.01-11.20(1 H, s, COOH), 8.30-8.25(2 H, d, Ar-H), 7.69-7.42(3 H, m, Ar-H), 7.15(1 H, s, Ar-H),6.89(1 H, d, Ar-H), 6.69(s, 1H, Ar-H), 4.01-4.09(3 H, d, CH_2), 3.92(12 H, s, OCH_3), 2.79(2H, d CH_2); ^{13}C NMR: 191.5, 168.1, 165.5, 153.4, 142.6, 141.5, 137.3, 136.7, 134.1, 133.2, 130.3, 126.7, 126.5, 126.3, 125.0, 119.2, 111.7, 106.6, 104.6, 60.8, 56.1, 55.8, 53.8, 36.6,31.6, 30.0; MS, *m/z*: 533.25 (*M*+). Anal. Calcd. For $C_{29}H_{27}NO_7S$: C, 65.28; H, 5.10; O, 20.99; S, 6.01; Found: C, 65.27; H, 5.16; O, 20.98; S, 6.03 %.

2-((6-amino-3-cyano-1-oxo-4-(3,4,5-trimethoxyphenyl)-1,2,3,4-tetrahydronaphthalen-2-yl)methyl)thio)benzoic acid (10g)

^{1}H NMR: 11.01-11.02(1 H, s, COOH), 8.30-8.25(2 H, d, Ar-H), 7.69-7.28 (3 H, m, Ar-H), 7.09(1 H, s, Ar-H), 6.70(2 H, s, Ar-H), 6.30(2 H, s, NH), 6.27-6.24(3 H, t, Ar-H), 4.02-4.05(3 H, d, CH_2), 3.93(9 H, s, OCH_3), 2.79(2H, d CH_2);^{13}C NMR: 191.5, 168.1, 153.4, 153.3, 142.6, 141.3, 137.3, 136.7, 134.1, 133.2, 130.1, 126.7, 126.5, 125.0, 124.0, 119.2, 111.6, 115.1, 106.6, 60.8, 56.1, 53.8, 36.6,31.6, 30.0; MS, *m/z*: 519.15 (*M*+). Anal. Calcd. For $C_{28}H_{26}N_2O_6S$: C, 64.85; H, 5.05; O, 18.51; S, 6.18; Found: C, 64.87; H, 5.06; O, 18.50; S, 6.18 %.

CONCLUSION

A facile and one pot synthesis of 2-[(3-cyano-1-oxo-4-(3, 4, 5-trimethoxyphenyl)-1, 2, 3, 4-tetrahydronaphthalen-2-yl) thio] benzoic acid derivatives was achieved with an excellent yield.

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