Bioorganic & Medicinal Chemistry Letters 23 (2013) 6127–6133

Contents lists available at ScienceDirect

Bioorganic & Medicinal Chemistry Letters

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

Restraining the flexibility of the central linker in terameprocol results in constrained analogs with improved growth inhibitory activity

Sherman Si Han Ho, Mei Lin Go *

Department of Pharmacy, National University of Singapore, 18 Science Drive 4, Singapore 117543, Republic of Singapore

ARTICLE INFO

Article history:
Received 14 June 2013
Revised 12 August 2013
Accepted 5 September 2013
Available online 13 September 2013

Keywords:
Terameprocol
Constrained analogs
Growth inhibitory activity
Structure–activity relationship

ABSTRACT

The semi-synthetic lignan terameprocol inhibits the transcription of several inflammatory and oncogenic genes and has been evaluated for its anti-cancer properties. Here we investigated the effect of restricting the flexibility of the carbon linker connecting the terminal rings of terameprocol on its growth inhibitory activity. Conformational restriction was explored by introducing unsaturation, inserting polar entities with limited flexibility and cyclization of the connecting linker. Twenty three compounds were synthesized and evaluated on a panel of malignant human cells. The most promising compounds were those with non-polar linkers, as seen in butadiene **1a** and the cyclized benzylideneindane analog **7**. Both compounds were more potent than terameprocol on pancreatic BxPC-3 cells with GI_{50} values of 3.4 and 8.1 μM, respectively. Selected isomers of **1a** (*E*,*E*) and **7** (*Z*) adopted low energy bent conformations that mimicked the low energy conformer of terameprocol. It is tempting to propose that conformational similarity to terameprocol may have contributed to their good activity. The scaffolds of **1a** and **7** should be further investigated for their anticancer potential.

Nordihydroguaiaretic acid (NDGA) is a naturally occurring lignan found in the dried leaves and resin of the creosote bush (*Larrea divaricata*). NDGA is associated with a wide spectrum of biological activity[1] and its structural analogs have likewise been found to possess an impressive range of therapeutically relevant properties.[2] Terameprocol (meso-tetra-*O*-methyl nordihydroguaiaretic acid), also known as M4N or EM-1421, is arguably the best known and most widely investigated NDGA analog.[3–10] (Fig. 1) Terameprocol inhibited the transcription of several genes that are involved in carcinogenesis and inflammation. These include the Sp1-dependent genes that transcribe the anti-apoptotic protein survivin and the cell cycle protein cyclin dependent kinase cdc2.[8,9] It also suppressed the expression of inducible cyclooxygenase-2 (COX-2)[5] and inhibited nuclear factor kappa-B (NF-κB)-dependent transcription of several pro-inflammatory cytokines by preventing the binding of RelA, a transcription factor of the NF-κB family, to its cognate sites on DNA.[6]

There is limited information on the structure–activity relationship (SAR) of terameprocol with regards to its anti-cancer activity. Most investigations focussed on other NDGA analogs and activities that were not related to carcinogenesis.[11,12] Nonetheless, in those cases where anticancer activity was monitored, the structural similarity between terameprocol and NDGA allowed some broad deductions to be made.[11,13] It is likely that the methyl groups on the butane side chain linking the phenyl rings were not critical for anti-cancer activity. Compounds **I**, **II** and **III** which lacked methyl substituents on the connecting butane linker provided support for this notion (Fig. 1). Compound **I** (IC_{50} 0.3 μM) was at least 10 times more potent than NDGA (IC_{50} 4.4 μM) on the small lung cancer cell line H69.[13] Compounds **II** and **III** were singled out for detailed biological characterization in a patent on a large series of tetra-O-substituted butane bridge-modified NDGA analogs,[11] presumably due to their promising biological activities. Indeed, **III** was cited as the most potent survivin inhibitor among the investigated compounds.[11] It was also apparent from **II** and **III** that functionalization of the bis-catechol moieties to give ethers was well tolerated. Compound **IV** is a conformationally restricted analog of NDGA in which the butane linker is locked in a tetrahydronapthalene scaffold. This modification was deemed to have improved selectivity: **IV** was reported to inhibit the breast cancer target IGF-1R to a greater extent than 15-lipooxygenase, an off-target enzyme that was preferentially inhibited by NDGA.[14]

Conformational restriction is a widely employed optimization strategy in medicinal chemistry. It minimizes the loss of conformational entropy that is incurred when a ligand binds to its target because the rotatable bonds in a conformationally restricted analog, unlike its flexible counterpart, are pre-shaped for the binding interaction. Thus, there is a free energy advantage conferred by this modification, which could translate to greater binding affinity or

* Corresponding author. Tel./fax: +65 65162654.
E-mail address: phagoml@nus.edu.sg (M.L. Go).

0960-894X/$ - see front matter © 2013 Elsevier Ltd. All rights reserved.
http://dx.doi.org/10.1016/j.bmcl.2013.09.014

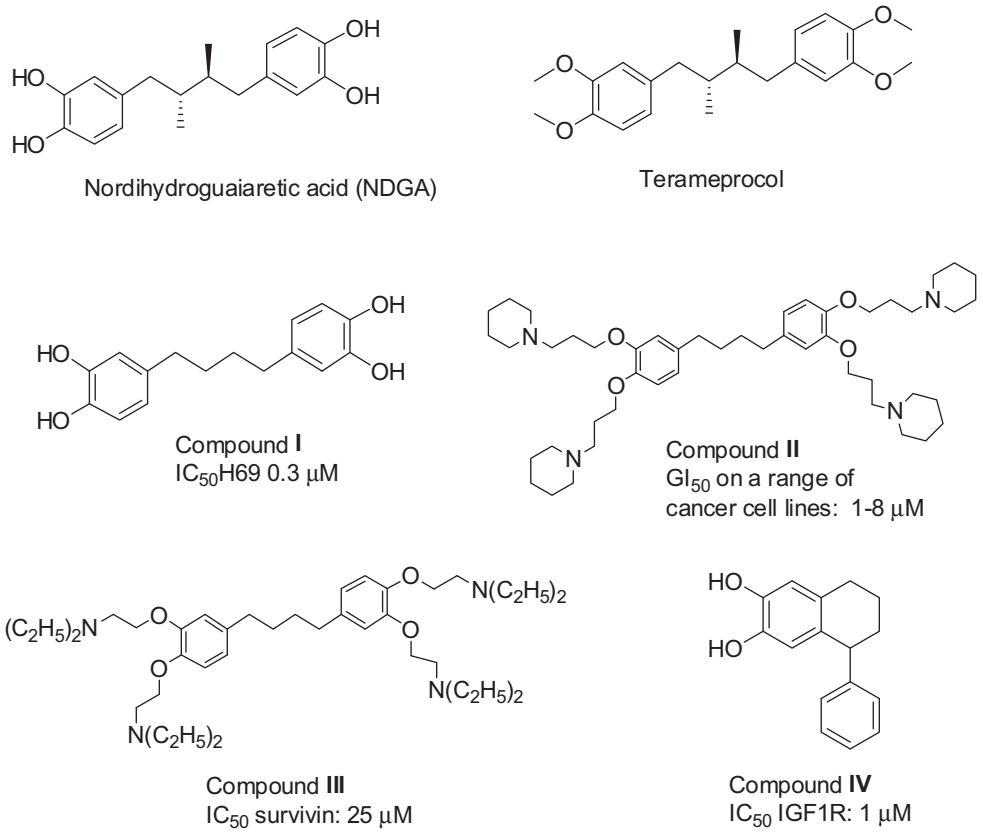


Figure 1. Structures of nordihydroguaiaretic acid (NDGA), terameprocol and compounds **I**–**VI**.

specificity. Besides **IV**, other conformationally restricted NDGA analogs have been reported, but not always in the context of anticancer activity.[12] In these compounds, the butane linker was restrained in furan or tetrahydrofuran or lactone rings.[12] Here, we report the syntheses and antiproliferative activities of conformationally restricted terameprocol analogs. Broadly, conformational restraint was imposed on the butane linker by (i) inclusion of conjugated double bonds (Series 1), (ii) insertion of a carbonylamino or sulfonylamino or ureido functionality (Series 2–4) and (iii) cyclization (Series 5, 6, compound **7** and ganschisandrine) (Fig. 2). The compounds were designed to retain the bis-3,4-dimethoxy substituted phenyl rings present in terameprocol. Electron delocalization in the polar carbonylamino, sulfonylamino and ureido moieties would restrict flexibility of the linker besides serving to reduce the lipophilic character of terameprocol (estimated *C*log*P* 5.76). Cyclization strategies were loosely based on **IV**, but included polar entities (sulfonylamino, carbonylamino) within the cyclized scaffold. A Scifinder Scholar search showed that all the compounds have been reported but only 9 compounds have citations for biological activity. The relevant references are given in the Supplementary data.

A total of 23 compounds were synthesized by conventional methods. The diphenylbutadiene **1a** was synthesized by a palladium-catalyzed Heck reaction between 3,4-dimethoxy-β-bromostyrene (**8**) and 3,4-dimethoxystyrene as detailed in Scheme 1.[15] The proton NMR spectra of **1a** indicated the presence of a single isomer, which was deduced to be *E*,*E* based on the symmetrical appearance of the two singlets attributed to the ring methoxy protons. Coupling constants could not be used for structure assignment of **1a** because one pair of vinylic protons was embedded with the aromatic protons while the two protons at the center of the butadiene linker exhibited complex splitting patterns due to long range coupling. The proton NMR spectra of **1a** is shown in Supplementary data. When **1a** was analyzed by HPLC, only a single peak was observed in the the chromatogram, which further supported the presence of a single isomer. Compound **8** was synthesized by a modified Hunsdiecker reaction from 3,4-dimethoxycinnamic acid.[16]

The acrylamides **1b**, **1c** were obtained by amide coupling in the presence of 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide (EDC) and 1-hydroxybenzotriazole (HOBt) (Scheme 2). The same reaction was used to prepare the amides **2a**–**2f** (Scheme 2).

The symmetrical ureas **3a** and **3c** were synthesized by refluxing urea with the corresponding amines,[17] whereas **3b** was afforded by the condensation of an amine with an isocyanate (Scheme 3).

Compounds **4a**–**4c** were obtained by reacting 3,4-dimethoxybenzenesulfonyl chloride with the respective amines (Scheme 4).

The constrained analogs of Series 5 were derived by incorporating the N of the carbonylamino (**5a**, **5b**) or sulfonylamino (**5c**) moiety in a tetrahydroisoquinoline ring. In **5d**, the sulfonyl moiety of **5c** was replaced by methylene. The Schotten–Baumann reaction between an acyl chloride and 3,4-dimethoxy-tetrahydroisoquinoline was employed for the syntheses of **5a** and **5b**.[19,20] The same tetrahydroisoquinoline was reacted with 3,4-dimethoxybenzenesulfonylchloride to give **5c**, and 3,4-dimethoxybenzyl bromide (**10**) in the presence of diisopropylethylamine (Huenig's base)[18] to give **5d** (Scheme 5).

In Series 6, the linker was incorporated in an isoquinoline ring as in Series 5, except that the dimethoxyphenyl ring was not attached directly to the heterocyclic nitrogen but at the α-carbon. Subjecting **2c** and **2f** to phosphoryl chloride in a microwave assisted Bischler–Naperialski reaction afforded dihydroisoquinolines **6a** and **6b**, respectively. Tetrahydroisoquinoline **6c** was synthesized by a microwave assisted Pictet–Spengler reaction with

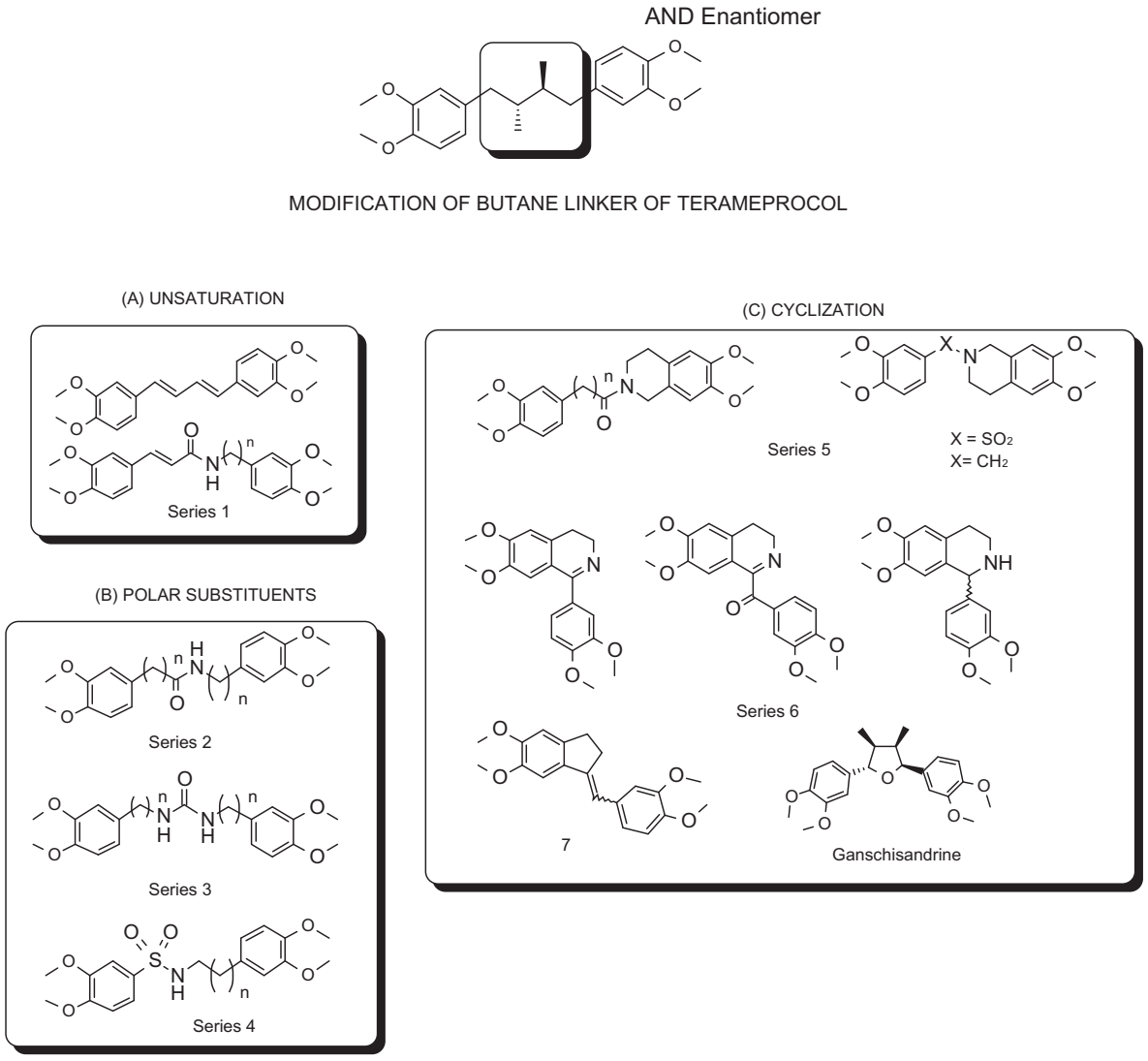
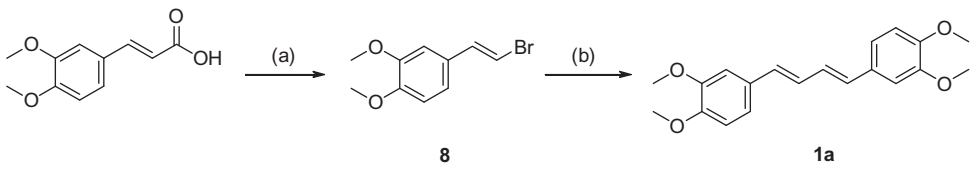


Figure 2. Conformational restriction of the butane linker in terameprocol by (A) Introducing unsaturation (Series 1, $n = 0, 1$); (B) inserting electron delocalized polar entities (Series 2–4, $n = 0, 1, 2$); (C) cyclization (Series 5, 6, compound **7**, ganschisandrine).



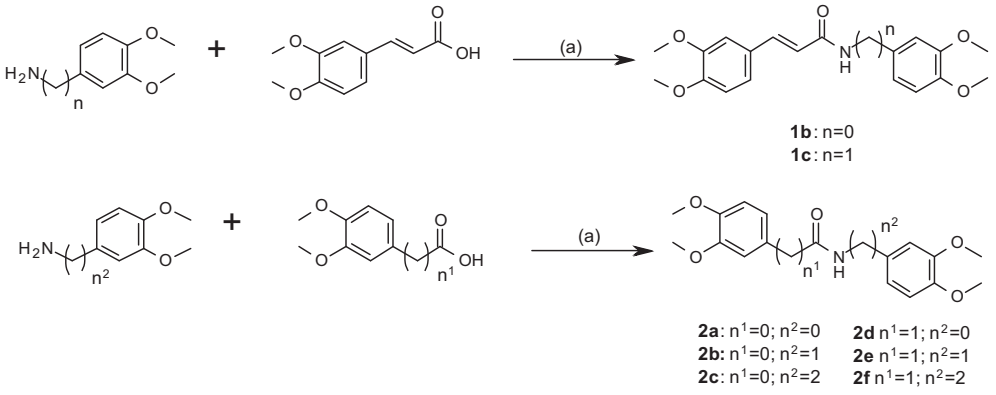
Scheme 1. Synthesis of **1a**. Reagents and conditions: (a) *N*-bromosuccinimide, triethylamine, CH_2Cl_2, rt, 0.5 h; (b) 3,4-dimethoxystyrene, $Pd(OAc)_2$, PPh_3, triethylamine, DMF, N_2, 110 °C, 5 h.

trifluoroacetic acid (Scheme 6).[19] The chiral forms of **6c** were not separated at this stage of the investigation.

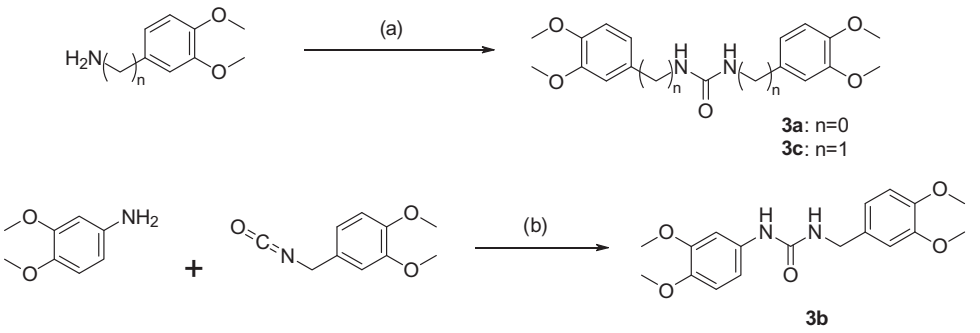
Compound **7** was prepared by the Wittig reaction between 5,6-dimethoxy-1-indanone and the triphenylphosphonium salt of 3,4-dimethoxybenzyl bromide (**11**) with sodium methoxide as base (Scheme 7). Both *E* and *Z* isomers of **7** were obtained in a ratio that was estimated from ^{1}H NMR to be 7:1, in favour of the *E* isomer. They were not separated at this stage of the investigation.

The compounds were evaluated for growth inhibitory activity (72 h) on a panel of human malignant cells: BxPC-3 (pancreatic adenocarcinoma), RCC786-0 (clear cell renal cell carcinoma), T47D (breast cancer), HeLa (cervical cancer), T98G and U87 (glioblastoma). Growth inhibitory activity was quantified as GI_{50} (concentration required to reduce viability to 50% of that observed in untreated controls, with readings corrected for cell count at time zero) using the 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) assay which is based on cellular redox enzyme activity (Table 1).

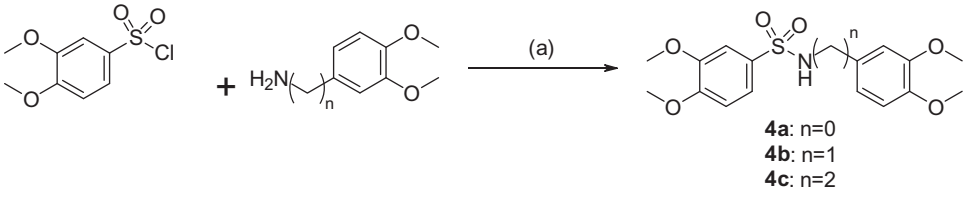
Terameprocol curtailed the proliferation of only three of the five cell lines investigated, namely pancreatic BxPC-3, renal RCC786-0 and breast T47D. Its GI_{50} on T47D and RCC786-0 were in the low micromolar range (≈5 μM), but it was less active on the pancreatic BxPC-3 cells (GI_{50} 17 μM). Ganschisandrine (Fig. 2) is a naturally occurring lignan structurally related to terameprocol as a



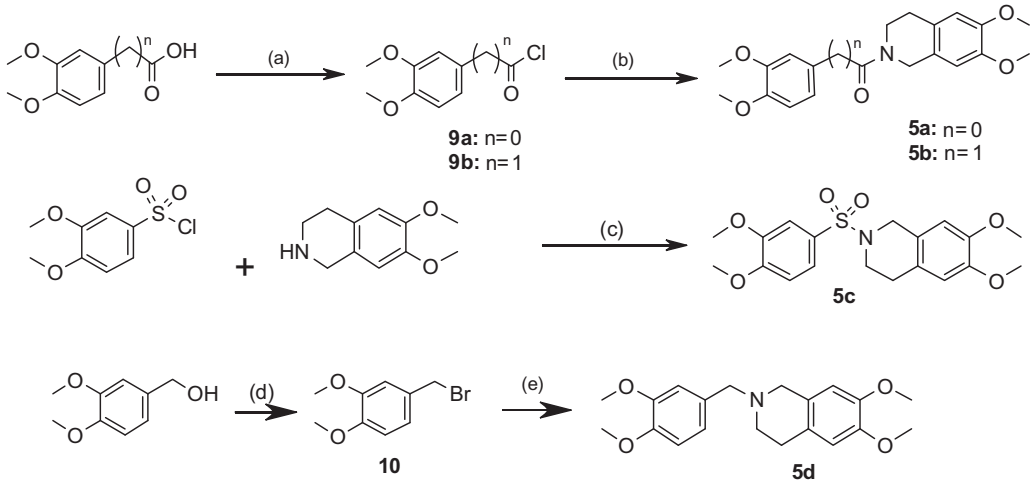
Scheme 2. Synthesis of **1b**, **1c**, **2a**–**2f**. Reagents and conditions: (a) EDC, HOBt, TEA, CH_2Cl_2, rt, 18 h.



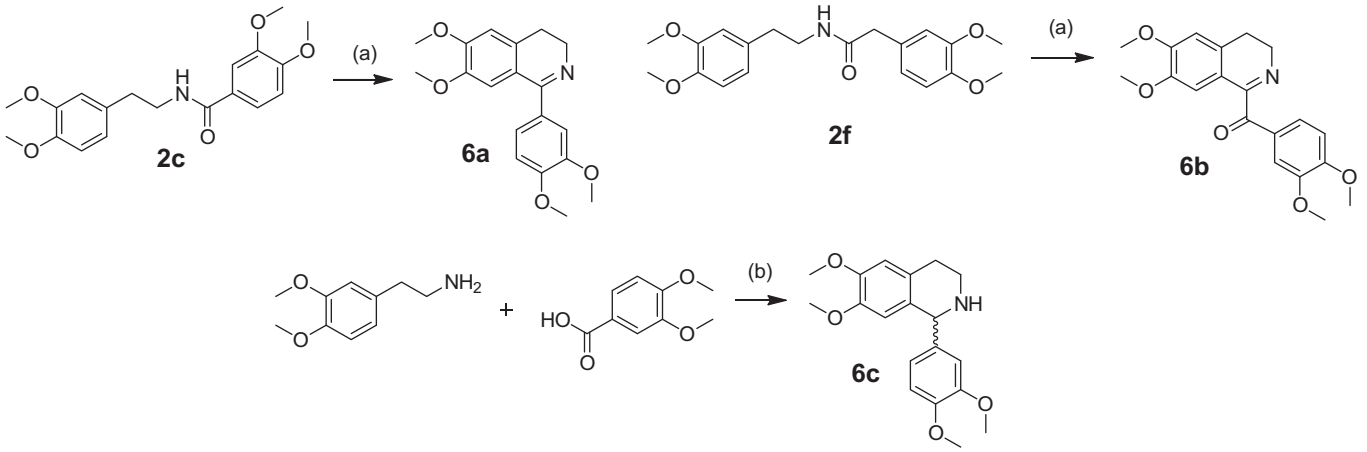
Scheme 3. Synthesis of **3a**–**c**. Reagents and conditions: (a) urea, 170 °C, 3.5 h; (b) THF, rt, 1 h.



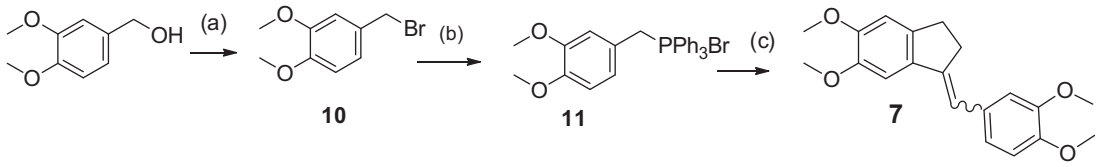
Scheme 4. Synthesis of **4a**–**4c**. Reagents and conditions: (a) TEA, CH_2Cl_2, rt, 0.5 h.



Scheme 5. Synthesis of **5a**–**5d**. Reagents and conditions: (a) $SOCl_2$, CH_2Cl_2, N_2, rt, 18 h; (b) 3,4-dimethoxy-1,2,3,4-tetrahydroisoquinoline HCl, NaOH, CH_2Cl_2, H_2O, rt, 3 h; (c) TEA, CH_2Cl_2, rt, 0.5 h; (d) PBr_3, CH_2Cl_2, rt, 24 h; (e) 3,4-dimethoxy-1,2,3,4-tetrahydroisoquinoline HCl, DIPEA, CH_3CN, N_2, rt, 4 h.



Scheme 6. Synthesis of **6a**–**6c**. Reagents and conditions: (a) $POCl_3$, toluene, mw 140 °C, 0.5 h; (b) TFA, toluene, mw 140 °C, 0.5 h.



Scheme 7. Synthesis of **5a**–**5d**. Reagents and conditions: (a) PBr_3, $CHCl_2$, rt, 24 h; (b) TPP, toluene, 110 °C, 18 h; (c) 5,6-dimethoxy-1-indanone, NaOMe, THF, N_2, 50 °C, 18 h.

Table 1
Growth inhibitory GI_{50} values of test compounds, terameprocol and ganschisandrine on malignant pancreatic BxPC-3, renal RCC786-0, breast T47D, cervical HeLa and glioblastoma T98G, U87 cells

Compound	Antiproliferative activity GI_{50}[a] (μM)					
	BxPC-3	RCC786-0	T47D	HeLa	T98G	U87
1a	3.41 ± 0.42	2.67 ± 0.48	>100	>100	>100	>100
1b	>50	>50	>50	>50	>50	>50
1c	>75	68.4 ± 5.9	>100	>75	70.3 ± 5.5	57.1 ± 1.0
2a	>100	>100	>100	>100	>100	>100
2b	>100	>100	>100	>100	>100	>100
2c	>100	>100	>100	>100	>100	>100
2d	>100	>100	>100	>100	>100	>100
2e	>100	>100	>100	>100	>100	>100
2g	>100	>100	>100	>100	>100	>100
3a	>50	>50	>50	>50	>50	>50
3b	>100	>100	>100	>100	>100	>100
3c	>100	>100	>100	>100	>100	>100
4a	>100	>100	>100	>100	>100	>100
4b	>100	>100	>100	>100	>100	>100
4c	>100	>100	>100	>100	>100	>100
5a	13. 6 ± 2.8	24.1 ± 4.1	11.9 ± 2.9	8.23 ± 0.32	10.1 ± 1.2	20.6 ± 3.3
5b	>100	>100	>100	>100	>100	>100
5c	>50	>50	>50	>50	>50	>50
5d	>100	>100	45.4 ± 6.4	55.9 ± 9.0	>100	>100
6a	>100	>100	>100	79.3 ± 16.3	>100	>100
6b	26.3 ± 5.5	>100	16.1 ± 1.5	16.9 ± 3.9	>100	>100
6c	>100	>100	>100	57.6 ± 11.1	>100	>100
7[b]	8.10 ± 2.19	5.50 ± 1.22	4.24 ± 0.63	>25	>25	>25
Terameprocol	17.1 ± 4.0	4.54 ± 0.98	5.36 ± 1.04	>50	>50	>50
Ganschisandrine	17.2 ± 1.8	>75	4.40 ± 0.46	>75	58.3 ± 1.1	>75

[a] Mean ± standard deviation of $n \geqslant 3$ determinations. GI_{50} was determined from the expression: $T - T_o/C - T_o = 50\%$ where T = absorbance at 72 h of cells exposed to test compound, T_o = absorbance at 0 h, C = absorbance at 72 h of untreated cells. Absorbance readings were obtained from MTT assay.
[b] Compound **7** had low solubility and antiproliferative activity could not be determined beyond 25 μM.

constrained analog. It retains several features of terameprocol, namely the terminal dimethoxyphenyl rings, the four carbon separation between the phenyl rings and methyl substitution of the ring/linker.It was equipotent to terameprocol on T47D and BxPC-3 but significantly less potent on RCC786-0 (GI_{50} >75 μM). The latter notwithstanding, it may be inferred that restraining the butane linker in a tetrahydrofuran ring did not abolish growth inhibitory activity. We also found that the most stable conformer of terameprocol, identified from a conformational search on MOE (Molecular Operating Environment, 2011.10), was folded with the terminal phenyl rings oriented orthogonally to each other (Fig. 3A). Thus, cyclization of the linker may provide a means of mimicking the

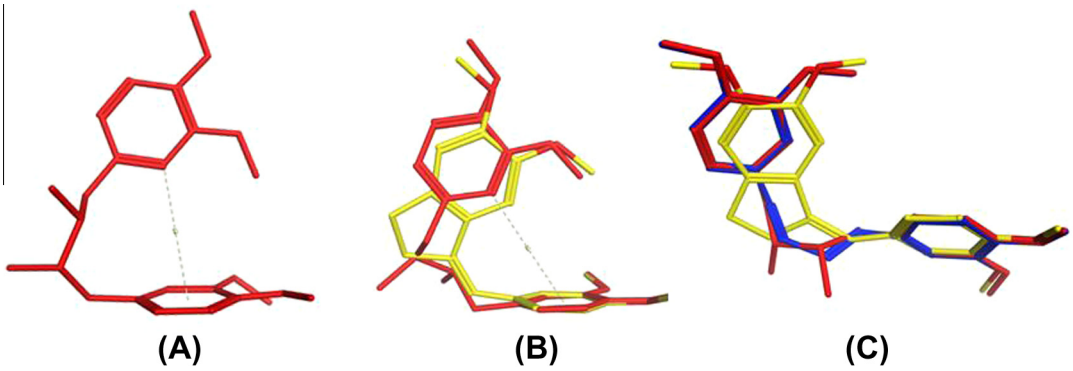


Figure 3. (A) Stable conformer of terameprocol identified from conformational search on MOE (Molecular Operating Environment, Version 2011.10). Method: LowModeMD, RMS gradient 0.005, number of iterations 10,000. (B) Flexible alignment of terameprocol (red) and **7Z** (yellow) by MOE (flexible alignment mode, 200 iterations, failure rate 20, energy cutoff 15 kcal/mol). Dotted lines depict Van der Waals interactions between the methyl and phenyl rings. (C) Overlapping stable conformers of **1a** (*E,E,* ciscoid) (blue), **7Z** (yellow) and terameprocol (red) as determined by flexible alignment MOE. A conformational search showed that the energy of **1a** (*E,E* ciscoid) was 98.37 kcal/mol compared to 95.79 kcal/mol for the stable conformer of **1a** (*E,E* transoid).

energetically more stable, and possibly, biologically relevant conformer of terameprocol.

Of the synthesized compounds, only four compounds (**1a**, **5a**, **6b** and **7**) had one or more GI_{50} values that were lower than those of terameprocol. Compounds in Series **2**, **3** and **4** were devoid of growth inhibitory properties. This may indicate that limiting the rotational flexibility of the carbonylamino, sulfonylamino and ureido groups in **2**, **3** and **4**, respectively, gave rise to unfavourable conformations, or that the polarity introduced by these residues had an adverse effect on activity.

Cyclization in **5a** and **6b** was achieved by incorporating a tetrahydro or dihydroisoquinoline ring in the linker. Compound **5a** was more potent than **6b** on BxPC-3, T47D and Hela cells but it fared less well when compared to **1a** and **7**. The most outstanding feature of **5a** was its widespread growth inhibitory activity—it was active on all 5 cell lines with GI_{50} values ranging from 8 to 24 μM. A comparison with other compounds in Series 5 highlighted the importance of the amide carbonyl in linking the two rings of **5a**. Notably, a one-carbon extension of the linker (**5b**), replacing carbonyl with the isosteric sulfonyl (**5c**) or methylene (**5d**) significantly reduced growth inhibitory activity.

Among the actives with a cyclized feature, **7** had outstanding growth inhibitory activity. It was more potent than terameprocol on pancreatic BxPC-3 cells (GI_{50} 8.1 vs 17.1 μM for terameprocol) and equipotent on renal RCC786-0 and breast T47D cells (GI_{50} 4–5 μM). Interestingly, the most stable conformer of terameprocol and the *Z* isomer of **7** were remarkably well aligned when these molecules were tested for overlap using the Flexible Alignment module in MOE (Fig. 3A and B). As mentioned earlier, **7** was obtained as a mixture of *E* and *Z* isomers, with *E* the dominant isomer. Equilibria between *E* and *Z* isomers of 3-substituted indolin-2-ones have been reported[20] and it is conceivable that a similar *E*/*Z* isomerisation may have occurred in the structurally related **7**. If this results in the enrichment of **7Z** in the biological milieu, the good activity of **7** may derive in part from its ability to mimic the bent conformation of terameprocol.

The most active analog identified in this investigation was the butadiene **1a** which had outstanding growth inhibitory activities on BxPC-3 and RCC786-0 cells ($GI_{50} \approx 3$ μM). Notwithstanding its good activity profile, **1a** is a structural anomaly as it is unique among the other actives in lacking a cyclized feature. Conformational search identified the linear transoid *E,E* isomer of **1a** as the most stable conformer (95.79 kcal/mol) but **1a** had an energetically viable bent ciscoid *E,E* form (98.37 kcal/mol). This conformer could be reasonably aligned to terameprocol and **7Z**, with the three structures retaining the bent shape of the stable terameprocol conformer (Fig. 3C).

Aside from shape considerations, the lipophilicity of the synthesized compounds was also considered to determine its contribution to activity. Based on their *C*log*P* values (Supplementary data), there was an apparent trend between lipophilicity and growth inhibitory activity. Among the synthesized compounds, the potent analogs **1a** and **7** were the most lipophilic (*C*log*P* 4.35 and 4.25, respectively) while the inactive Series 2–4 compounds were at least a hundred fold less lipophilic (*C*log*P* values <2.7). As conformational restraint in the latter compounds was achieved by incorporating polar carbonylamino, sulfonylamino and ureido functionalities, the concurrent fall in lipophilicity may have had an overriding adverse effect on activity. Nonetheless, it was gratifying to note that analogs (**1a**, **7**) with greater potency and lesser lipophilic character than terameprocol (*C*log*P* 5.76) could be obtained by the present approaches.

Taken together, we have shown here that restricting the conformational flexibility of the connecting linker in terameprocol is a viable means of improving growth inhibitory activity against a panel of malignant cells. Restraining flexibility by incorporating unsaturation (**1a**) and cyclization coupled with unsaturation (**7**) yielded promising results. Selected isomers of **1a** and **7** mimicked the bent shape found in the lowest energy conformer of terameprocol. Their scaffolds warrant further investigation to determine if their biological targets coincided with that of terameprocol and if additional functionalization could lead to improved in vitro and in vivo growth inhibitory activities.

Acknowledgments

Sherman S.H. Ho gratefully acknowledges National University of Singapore for the President's Graduate Fellowship. The work is supported by a research grant from the National University of Singapore (RP 148 000 171 112) to M.L. Go.

Supplementary data

Supplementary data (details on the growth inhibitory assay, spectral characteristics and *C*log*P* values of synthesized compounds are provided) associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.bmcl.2013.09.014.

References and notes

1. Lambert, J. D.; Dorr, R. T.; Timmermann, B. N. *Pharm. Biol.* **2004**, *42*, 149.
2. Saleem, M.; Kim, H. J.; Ali, M. S.; Lee, Y. S. *Nat. Prod. Rep.* **2005**, *22*, 696.
3. Hwu, J. R.; Tseng, W. N.; Gnabre, J.; Giza, P.; Huang, R. C. C. *J. Med. Chem.* **1998**, *41*, 2994.

4. Chen, H.; Teng, L.; Li, J. N.; Park, R.; Mold, D. E.; Gnabre, J.; Hwu, J. R.; Tseng, W. N.; Huang, R. C. C. *J. Med. Chem.* **1998**, *41*, 3001.
5. Eads, D.; Hansen, R. L.; Oyegunwa, A. O.; Cecil, C. E.; Culver, C. A.; Scholle, F.; Petty, I. T. D.; Laster, S. M. *J. Inflammatory (Lond)* **2009**, *6*.
6. Oyegunwa, A. O.; Sikes, M. L.; Wilson, J. R.; Scholle, F.; Laster, S. M. *J. Inflammatory (Lond)* **2010**, *7*.
7. Heller, J. D.; Kuo, J.; Wu, T. C.; Kast, W. M.; Huang, R. C. C. *Cancer Res.* **2001**, *61*, 5499.
8. Chang, C. C.; Heller, J. D.; Kuo, J.; Huang, R. C. C. *Proc. Natl. Acad. Sci. USA* **2004**, *101*, 13239.
9. Li, F.; Altieri, D. C. *Cancer Res.* **1999**, *59*, 3143.
10. Park, R.; Chang, C. C.; Liang, Y. C. *Clin. Cancer Res.* **2005**, *11*, 4601.
11. Huang, R. C.; Baltimore, M. D.; Kotohiko, K. US20110014192, **2011**.
12. Chen, Q. *Curr. Top. Med. Chem.* **2009**, *9*, 1636.
13. McDonald, R. W.; Bunkobpon, W.; Liu, T.; Fessler, S.; Pardo, O. E.; Freer, I. K. A.; Glaser, M.; Seckl, M. J.; Robins, D. J. *Anticancer Drug Des.* **2001**, *16*, 261.
14. Blecha, J. E.; Anderson, M. O.; Chow, J. M.; Guevarra, C. C.; Pender, C.; Penaranda, C.; Zavodovskaya, M.; Youngren, J. F.; Berkman, C. E. *Bioorg. Med. Chem. Lett.* **2007**, *17*, 4026.
15. Dieck, H. A.; Heck, R. F. *J. Am. Chem. Soc.* **1974**, *96*, 1133.
16. Das, J. P.; Roy, S. *J. Org. Chem.* **2008**, *67*, 7861.
17. Baeyer, A. *Justus Liebigs Ann. Chem.* **1864**, *131*, 251.
18. Moore, J. L.; Taylor, S. M.; Soloshonok, V. A. *ARKIVOC* **2005**, *6*, 287.
19. Awuah, E.; Capretta, A. *J. Org. Chem.* **2010**, *75*, 5627.
20. Sun, L.; Tran, N.; Tang, F.; App, H.; Hirth, P.; McMahon, G.; Tang, C. *J. Med. Chem.* **1998**, *41*, 2588.