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Synthesis and antiproliferative evaluation of 13-aryl-13*H*-benzo[*g*]-benzothiazolo [2,3-*b*]quinazoline-5,14-diones

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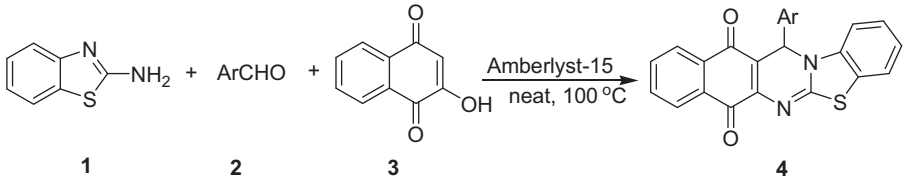
ABSTRACT

A simple synthesis of novel 13-aryl-13*H*-benzo[*g*]benzothiazolo [2,3-*b*]quinazoline-5,14-dione derivatives was accomplished in excellent yields via the reaction of 2-aminobenzothiazole, aromatic aldehydes and 2-hydroxy-1,4-naphthoquinone in the presence of amberlyst-15. The antiproliferative activities of all the synthesized compounds were assessed on two different human cancer cell lines (HepG2 and Hela), and the results showed that most of the new compounds showed good to potent cytotoxic activities.

The 1,4-naphthoquinone ring is a key structural unit for numerous natural products,[1] synthetic pharmaceuticals.[2] Structures embedded with 1,4-naphthoquinone units display potential medicinal properties such as anticancer,[3] antifungal,[4] antibacterial,[5] antiviral,[6] anti-inflammatory,[7] antimalaria,[8] antiplatelet,[9] antithrombotic,[10] antiallergic,[11] apoptotic[12] and lipoxygenase inhibiting[13] activities. Furthermore, 1,4-naphthoquinones have also been shown to inhibit human DNA topoisomerase.[14] A number of 1,4-naphthoquinone derivatives having nitrogen atom present in them received a great deal of attention for their anticancer activity.[3e,5c,15] Therefore, the development of facile approaches to access these novel targets with structural diversity is highly desirable and valuable for medicinal chemistry and drug discovery.

Multicomponent reactions (MCRs) typically involve more than two reactants to combine in a sequential manner giving highly selective products while retaining majority of the atoms of the starting material. MCRs have received considerable attention because of its wide range of applications in pharmaceutical chemistry for the creation of structural diversity and combinatorial libraries for drug discovery.[16]

In recent years, the use of solid acidic catalysts has offered important advantages in organic synthesis, for example, operational simplicity, environmental compatibility, nontoxic, reusability, low cost and ease of isolation. A tremendous upsurge of interest in various chemical transformations processes by catalysts under heterogeneous conditions has occurred. One of those heterogeneous catalysts is amberlyst-15. It makes reaction processes convenient, more economic and environmentally benign. Owing to the numerous advantages associated with this cheap and non-hazardous catalyst, amberlyst-15 has been explored as a powerful



Scheme 1. Synthesis of 13-aryl-13*H*-benzo[*g*]benzothiazolo [2,3-*b*]quinazoline-5,14-diones using amberlyst-15 as a catalyst.

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Table 1
Optimization of the reaction conditions for three-component synthesis of 13-phenyl-13*H*-benzo[*g*]benzothiazolo [2,3-*b*]quinazoline-5,14-dione[a]

Entry	Catalyst (mol %)	Time (h)	Yield[b] (%)
1	Amberlyst-15 (10)	10	87
2	$InCl_3$ (10)	2	51
3	$ZrOCl_4$ (10)	2	63
4	$ZnCl_2$ (10)	5	39
5	TFA (10)	2	67
6	*p*-TsOH (10)	2	78
7	Sulfamic acid (10)	2	74
8	Silica sulfuric acid (10)	2	69

[a] Reaction conditions: 2-aminobenzothiazole (1 mmol), benzaldehyde (1 mmol), 2-hydroxy-1,4-naphthoquinone (1 mmol); 100 °C; neat.
[b] Isolated yield.

Table 2
Preparation of 13-aryl-13*H*-benzo[*g*]benzothiazolo [2,3-*b*]quinazoline-5,14-diones[a]

Entry	Ar	Time (h)	Product	Yield[b] (%)
1	C_6H_5	2	**4a**	87
2	4-F–C_6H_4	2	**4b**	85
3	4-Me–C_6H_4	1.5	**4c**	93
4	2,5-$(MeO)_2$–C_6H_3	3	**4d**	85
5	3,4,5-$(MeO)_3$–C_6H_2	3	**4e**	90
6	4-NO_2–C_6H_4	1.5	**4f**	89
7	2,4-Cl_2–C_6H_3	3	**4g**	79
8	4-Cl–C_6H_4	2	**4h**	88
9	2-Furanyl	3	**4i**	82
10	2-Thiophenyl	3	**4j**	84

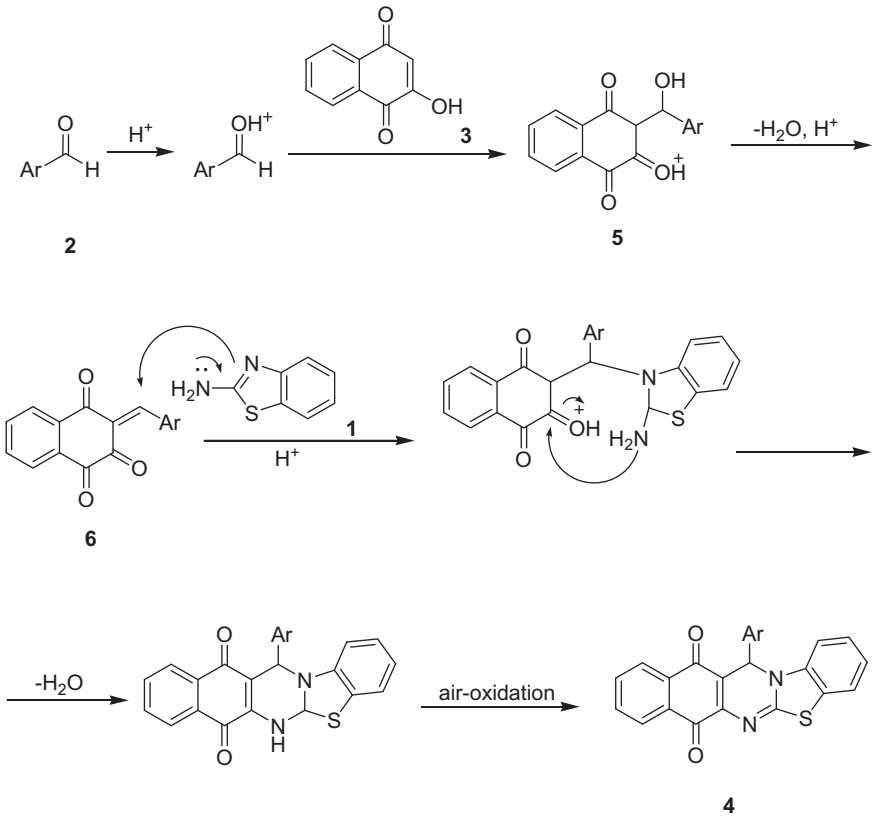
[a] Reaction conditions: 2-aminobenzothiazole (1 mmol), aldehyde (1 mmol), 2-hydroxy-1,4-naphthoquinone (1 mmol), amberlyst-15 (0.1 mmol); 100 °C; neat.
[b] Isolated yield.

catalyst for various organic transformations under mild conditions.[17]

As a consequence of our continued interest in the synthesis of novel heterocycles employing domino protocols,[18] herein we report for the first time a facile synthesis of a library of novel 13-aryl-13*H*-benzo[*g*]benzothiazolo [2,3-*b*]quinazoline-5,14-diones via the one-pot three-component domino reactions of 2-aminobenzothiazole, aromatic aldehydes and 2-hydroxy-1,4-naphthoquinone in the presence of amberlyst-15 (Scheme 1). Most importantly, these previously unreported novel series of 1,4-naphthoquinone derivatives having azacyclo exhibited different range of significant cytotoxic activities varying from 1.66 to 189.59 μM due to structural differences. It was worthwhile to note that all these compounds had lesser cytotoxicity on non-cancerous HEK 293 cells.

At the outset, the reaction of 2-aminobenzothiazole (1 mmol), benzaldehyde (1 mmol) and 2-hydroxy-1,4-naphthoquinone (1 mmol) was selected as a template reaction to investigate the catalyst effect at 100 °C under solvent-free conditions (Table 1, entries 1–8). A comparison of catalytic activity between Brønsted and Lewis acids showed highest catalytic activity of amberlyst-15 under solvent-free conditions at 100 °C (Table 1, entry 1).

Based on the optimized reaction conditions, a series of 13-aryl-13*H*-benzo[*g*]benzothiazolo [2,3-*b*]quinazoline-5,14-diones were synthesized. The results, summarized in Table 2, showed that the three-component reaction in the presence of amberlyst-15 gave the corresponding products in moderate to good yields. This methodology can be applied to aromatic aldehydes either with electron-withdrawing groups (such as, nitro, halogen) or electron-donating groups (such as, methoxy, methyl) with excellent yields under the same conditions. Therefore, we conclude that the electronic nature of substituents of the aromatic aldehyde had no significant effect on the reaction. Even the heterocyclic aldehyde could be used in



Scheme 2. A plausible mechanistic pathway to explain the amberlyst-15 catalyzed formation of compounds **4**.

Table 3
Antiproliferative activities of 13-aryl-13*H*-benzo[*g*]benzothiazolo [2,3-*b*]quinazoline-5,14-diones

Compd	IC_{50}[a] (μM)		
	HepG2	Hela	HEK293
4a	1.66 ± 0.92	2.99 ± 0.39	4.16 ± 0.17
4b	9.4 ± 0.45	3.96 ± 0.16	15.08 ± 0.67
4c	1.70 ± 0.11	3.81 ± 0.08	5.18 ± 0.13
4d	189.59 ± 13.52	124.61 ± 2.31	>200
4e	5.03 ± 0.21	9.32 ± 0.38	11.04 ± 0.46
4f	14.33 ± 0.60	29.04 ± 1.08	50.34 ± 2.88
4g	3.56 ± 0.96	2.68 ± 0.21	4.90 ± 1.06
4h	23.42 ± 3.12	15.57 ± 0.43	25.92 ± 2.89
4i	9.07 ± 0.76	6.62 ± 0.28	10.14 ± 0.87
4j	5.76 ± 0.43	4.23 ± 0.39	5.90 ± 0.54
Adriamycin	1.15 ± 0.03	1.31 ± 0.04	1.06 ± 0.05

[a] The means of triplicates ± SD.

this reaction (Table 2, entries 9 and 10). However, when the aliphatic aldehyde was applied to this reaction, no expected product was obtained. The structures of the isolated products **4** were deduced on the basis of IR, ^{1}H NMR, ^{13}C NMR, mass spectrometry and elemental analysis.[19] The IR spectrum of **4a** showed absorptions at 1688 and 1622 cm^{-1} indicating the presence of C=O and C=N-bonds, respectively. The mass spectrum of **4a** displayed the molecular ion $[M+H]^+$ peak at $m/z = 395$, which was consistent with the 1:1:1 adduct of 2-aminobenzothiazole, benzaldehyde and 2-hydroxy-1,4-naphthoquinone with the loss of two equivalent water molecule. The ^{1}H NMR spectrum of **4a** showed two doublet of doublets ($\delta = 8.42$ and 8.09 ppm, $J = 1.2$, 8.0 Hz) arising from the protons peri to the quinone C=O. A singlet was observed ($\delta = 6.77$ ppm) for the CH group of C-13 position. The ^{13}C NMR spectrum of **4a** showed characteristic signals at $\delta = 56.2$ ppm (due to the Ph–CH group), 179.8 and175.9 ppm (arising from the two nonequivalent carbonyl groups).

A proposed mechanism for the reaction is outlined in Scheme 2. It is highly probable that amberlyst-15 catalyzes the formation of a carbocation in a reversible reaction with the aromatic aldehyde. The higher reactivity of the carbocation compared with the carbonyl species is utilized to facilitate Knoevenagel condensation between arylaldehyde **2** and 2-hydroxy-1,4-naphthoquinone **3** via intermediate **5**, and after dehydration olefin **6** is produced. Subsequent Michael-type addition of 2-aminobenzothiazole **1** to the olefin followed by intramolecular nucleophilic cyclization, dehydration, and aromatization by air-oxidation affords the corresponding products **4**.

All the synthesized compounds were subjected to in vitro antiproliferative evaluation using the MTT assay in two human cancer cell lines representative of major cancer HepG2 (liver) and Hela (cervix), and IC_{50} (μM) are presented in Table 3. Except for compounds **4d**, **4f** and **4h**, most of the new compounds showed good to potent antiproliferative activity against the two human tumor cell lines. The results in Table 3 showed also some important structure–activity relationships (SARs) for this series of derivatives. First, the rotatability of the acyl substituent at the C-13 position appeared to have an important effect upon cytotoxicity. Compound with 2′, 5′-substituents on the phenyl ring (**4d**) showed reduced activity compared with non-substituted **4a** and other substituted **4b**, **4c**, **4e**, **4f, 4g, 4h, 4i** and **4j**. The wide activity range observed for compounds **4a**–**4j** (IC_{50} from 1.66 to >100 μM) indicated that the nature of substituents at the C-13 position markedly affected the activity profile of these compounds. Substitution of the electron-rich aromatic ring at the C-13 position confered far greater cytotoxicity in comparison with the substitution of the electron-rich aromatic ring at the C-13 position. It is worthwhile to note that all these compounds have lesser cytotoxicity on non-cancerous HEK 293 cells.

In summary, we have developed an efficient and simple procedure to generate 13-aryl-13*H*-benzo[*g*]benzothiazolo [2,3-*b*]quinazoline-5,14-dione derivatives via the amberlyst-15 catalyed three-component condensation of 2-aminobenzothiazole, aromatic aldehydes and 2-hydroxy-1,4-naphthoquinone. Moreover, the cytotoxic activities of these compounds were evaluated in vitro on two different cancer cell lines, and the results show that some compounds exhibited good antiproliferative activities against HepG2 and Hela.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.bmcl.2014.02.018.

References and notes

1. Papageorgiou, V. P.; Assimoponlou, A. N.; Couladouros, E. A.; Hepworth, D.; Nicolaou, K. C. *Angew. Chem., Int. Ed.* **1999**, *38*, 270.
2. (a) McBride, T. J.; Oleson, J. J.; Woolf, D. *Cancer Res.* **1966**, *26A*, 727; (b) Reich, E.; Goldbreg, I. H.; Rabinowitz, M. *Nature* **1962**, *196*, 743; (c) Keyes, S. R.; Loomis, R.; DiGiovanna, M. P.; Pritsos, C. A.; Rockwell, S.; Sartorelli, A. C. *Cancer Commun.* **1991**, *3*, 351; (d) Papageorgiou, V. P.; Assimopoulou, A. N.; Couladourous, E. A.; Hepworth, D.; Nicolaou, K. C. *Angew. Chem., Int. Ed.* **1999**, *38*, 270.
3. (a) Benites, J.; Valderrama, J. A.; Rivera, F.; Rojo, L.; Campos, N.; Pedro, M.; José Nascimento, M. S. *Bioorg. Med. Chem. Lett.* **2008**, *16*, 862; (b) Benites, J.; Valderrama, J. A.; Bettega, K.; Pedrosa, R. C.; Calderon, P. B.; Verrax, J. *Eur. J. Med. Chem.* **2010**, *45*, 605; (c) Yamashita, M.; Kaneko, M.; Iida, A.; Tokuda, H.; Nishimura, K. *Bioorg. Med. Chem. Lett.* **2007**, *17*, 6417; (d) da Silva, E. N.; Cavalcanti, B. C.; Guimarães, T. T.; Pinto Mdo, C.; Cabral, I. O.; Pessoa, C.; Costa-Lotufo, L. V.; de Moraes, M. O.; de Andrade, C. K.; Dos Santos, M. R.; de Simone, C. A.; Goulart, M. O.; Pinto, A. V. *Eur. J. Med. Chem.* **2011**, *46*, 399; (e) Hadden, M. K.; Hill, S. A.; Davenport, J.; Matts, R. L.; Blagg, B. S. *Bioorg. Med. Chem.* **2009**, *17*, 634; (f) Zakharova, O. A.; Goryunov, L. I.; Troshkova, N. M.; Ovchinnikova, L. P.; Shteingarts, V. D.; Nevinsky, G. A. *Eur. J. Med. Chem.* **2010**, *45*, 270; (g) Bringmann, G.; Zhang, G.; Hager, A.; Moos, M.; Irmer, A.; Bargou, R.; Chatterjee, M. *Eur. J. Med. Chem.* **2011**, *46*, 5778.
4. (a) Sahu, P. K.; Sahu, P. K.; Gupta, S. K.; Thavaselvam, D.; Agarwal, D. D. *Eur. J. Med. Chem.* **2006**, *41*, 773; (b) Tandon, V. K.; Maurya, H. K.; Mishra, N. N.; Shukla, P. K. *Bioorg. Med. Chem. Lett.* **2011**, *21*, 6398; (c) Kongkathip, N.; Kongkathip, B.; Siripong, P.; Sangma, C.; Luangkamin, S.; Niyomdecha, M.; Pattanapa, S.; Piyaviriyagul, S.; Kongsaeree, P. *Bioorg. Med. Chem.* **2003**, *11*, 3179; (d) Ryu, C. K.; Han, J. Y.; Jung, O. J.; Lee, S. K.; Lee, J. Y.; Jeong, S. H. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 679; (e) Ryu, C. K.; Chae, M. J. *Arch. Pharm. Res.* **2005**, *28*, 750.
5. (a) Inbaraj, J. J.; Chignell, C. F. *Chem. Res. Toxicol.* **2004**, *17*, 55; (b) Huang, S. T.; Kuo, H. S.; Hsiao, C. L.; Lin, Y. L. *Bioorg. Med. Chem.* **2002**, *10*, 1947; (c) Tandon, V. K.; Yadav, D. B.; Chaturvedi, A. K.; Shukla, P. K. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 3288; (d) Tandon, V. K.; Yadav, D. B.; Singh, R. V.; Chaturvedi, A. K.; Shukla, P. K. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 5324.
6. (a) Crosby, I. T.; Bourke, D. G.; Jones, E. D.; Jeynes, T. P.; Cox, S.; Coates, J. A. V.; Robertson, A. D. *Bioorg. Med. Chem. Lett.* **2011**, *21*, 1644; (b) Jin, Y. R.; Ryu, C. K.; Moon, C. K.; Cho, M. R.; Yun, Y. P. *Pharmacology* **2004**, *70*, 195; (c) Zhang, Y. H.; Chung, K. H.; Ryu, C. K.; Ko, M. H.; Lee, M. K.; Yun, Y. P. *Biol. Pharm. Bull.* **2001**, *24*, 618.
7. (a) Sasaki, K.; Abe, H.; Yoshizaki, F. *Biol. Pharm. Bull.* **2002**, *25*, 669; (b) Lien, J. C.; Huang, L. J.; Teng, C. M.; Wang, J. P.; Kuo, S. C. *Chem. Pharm. Bull.* **2002**, *50*, 672; (c) Huang, L. J.; Chang, F. C.; Lee, K. H.; Wang, J. P.; Teng, C. M.; Kuo, S. C. *Bioorg. Med. Chem.* **1998**, *6*, 2261.
8. dos Santos, E. V. M.; Carneiro, J. W. D. M.; Ferreira, V. F. *Bioorg. Med. Chem.* **2004**, *12*, 87.
9. (a) Lien, J. C.; Huang, L. J.; Wang, J. P.; Teng, C. M.; Lee, K. H.; Kuo, S. C. *Chem. Pharm. Bull.* **1996**, *44*, 1181.
10. Yuk, D. Y.; Ryu, C. K.; Hong, J. T.; Chung, K. H.; Kang, W. S.; Kim, Y.; Yoo, H. S.; Lee, M. K.; Lee, C. K.; Yun, Y. P. *Biochem. Pharmacol.* **2000**, *60*, 1001.
11. Huang, L. J.; Chang, F. C.; Lee, K. H.; Wang, J. P.; Teng, C. M.; Kuo, S. C. *Bioorg. Med. Chem.* **1998**, 2261.

12. (a) Kim, H. J.; Kang, S. K.; Mun, J. Y.; Chun, Y. J.; Choi, K. H.; Kim, M. Y. *FEBS Lett.* **2003**, *555*, 217; (b) Gao, D.; Hiromura, M.; Yasui, H.; Sakurai, H. *Biol. Pharm. Bull.* **2002**, *25*, 827.
13. (a) Richwien, A.; Wurm, G. *Pharmazie* **2004**, *59*, 163; (b) Wurm, G.; Schwandt, S. *Pharmazie* **2003**, *58*, 531.
14. (a) Song, G. Y.; Kim, Y.; You, Y. J.; Cho, H.; Kim, S. H.; Sok, D. E.; Ahn, B. Z. *Arch. Pharm. Pharm. Med. Chem.* **2000**, *333*, 87; (b) Chae, G. H.; Song, G. Y.; Kim, Y.; Cho, H.; Sok, D. E.; Ahn, B. Z. *Arch. Pharm. Res.* **1999**, *22*, 507; (c) Song, G. Y.; Zheng, X. G.; Kim, Y.; You, Y. J.; Sok, D. E.; Ahn, B. Z. *Bioorg. Med. Chem. Lett.* **1999**, *9*, 2407.
15. (a) Lee, E. J.; Lee, H. J.; Park, H. J.; Min, H. Y.; Suh, M. E.; Chung, H. J.; Lee, S. K. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 5175; (b) Lee, H. J.; Park, S. Y.; Kim, J. S.; Song, H. M.; Suh, M. E.; Lee, C. O. *Bioorg. Med. Chem.* **2003**, *11*, 4791.
16. Zhu, J.; Bienayme, H. *Multi-Component Reactions*; Wiley: Weinheim, 2005.
17. (a) Mirjalili, B. B. F.; Zaghaghi, Z. *J. Chin. Chem. Soc.* **2008**, *55*, 694; (b) Meuzelaar, G.; Maat, L.; Sheldon, R.; Kozhevnikov, I. V. *Catal. Lett.* **1997**, *45*, 249; (c) Kozhevnikova, E. F.; Rafiee, E.; Kozhevnikov, I. V. *Appl. Catal.* **2004**, *A260*, 25; (d) Mao, J.; Nakajo, T.; Okuhara, T. *Chem. Lett.* **2002**, 1104; (e) Wu, L.-Q.; Yang, C.-G.; Zhong, C.; Yang, L.-M. *Bull. Korean Chem. Soc.* **2009**, *30*, 1665.
18. (a) Wu, L. Q.; Zhang, C.; Li, W. L. *Bioorg. Med. Chem. Lett.* **2013**, *23*, 5002; (b) Wu, L. Q. *Appl. Organomet. Chem.* **2013**, *27*, 148; (c) Yang, X. J.; Yang, L. M.; Wu, L. Q. *Bull. Korean Chem. Soc.* **2012**, *33*, 714; (d) Wu, L. Q.; Zhang, J. L.; Fang, L. Z.; Yang, C. G.; Yan, F. L. *Dyes Pigments* **2010**, *86*, 93.
19. The experimental procedures of synthesis and the spectroscopic data of the synthesized compounds are available in Supplementary data.