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Synthesis of new mixed phenol/heterocyclic derivatives and studies of their activity as inhibitors of Bax/Bcl-xL interaction

Duc Duy Vo [a], Fabien Gautier [b,c,d], Sophie Barillé-Nion [b], Philippe Juin [b,c], Nicolas Levoin [e], René Grée [a,*]

[a] Université de Rennes 1, Institut des Sciences Chimiques de Rennes, CNRS UMR 6226, Avenue du Général Leclerc, 35042 Rennes Cedex, France
[b] UMR 892 INSERM/6299 CNRS/Université de Nantes, Team 8 "Cell Survival and Tumor Escape in Breast Cancer", Institut de Recherche Thérapeutique de l'Université de Nantes, 8 quai Moncousu, BP 70721, 44007 Nantes Cedex 1, France
[c] Institut de Cancérologie de l'Ouest, Centre de Lutte contre le Cancer René Gauducheau, Boulevard Jacques Monod, 44805 Saint Herblain-Nantes Cedex, France
[d] Plateforme IMPACT, Biogenouest Institut de Recherche Thérapeutique de l'Université de Nantes, 8 quai Moncousu, BP 70721, 44007 Nantes Cedex 1, France
[e] Bioprojet-Biotech, 4 rue du Chesnay Beauregard, BP 96205, 35762 Saint Grégoire, France

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ABSTRACT

We describe here the synthesis of a series of new molecules containing phenol and heteroaromatic moieties, compounds, which have been evaluated for their ability to inhibit Bax/Bcl-xL interactions in BRET assays. Among them, a triazole derivative **13**, exhibit a very promising activity, being more potent than the reference compounds acylpyrogallol **1** and ABT 737. These preliminary results demonstrate that derivatives of this family can be attractive to develop new molecules with potent anticancer activity.

1. Introduction

Escape from apoptosis by cancer cells is considered as a very important contribution to carcinogenesis.[1] The overexpression of the antiapoptotic Bcl-2 family of proteins (typically Bcl-2, Bcl-xL, Mcl-1) is frequently observed in cancer cells and is implicated in their aberrant survival and their resistance to current treatments.[2] Inhibition of apoptosis by Bcl-2 homologs relies in great part on their ability to physically interact with proapoptotic members of the Bcl-2 family, the multi-domain proteins Bax and Bak and their upstream effectors the BH3-only proteins. Thus, antiapoptotic Bcl-2 proteins inhibitors, such as ABT 737 and its orally available equivalent, navitoclax that disrupt these interactions in cancer cells, are of therapeutic interest as they are expected to trigger cell death by themselves and/or to sensitize cells to chemotherapy.[3–5] Bcl-xL expression, in particular, is a marker of chemoresistance[6] and its interaction with Bax is critical to maintain cancer cell survival[7,8] (Fig. 1).

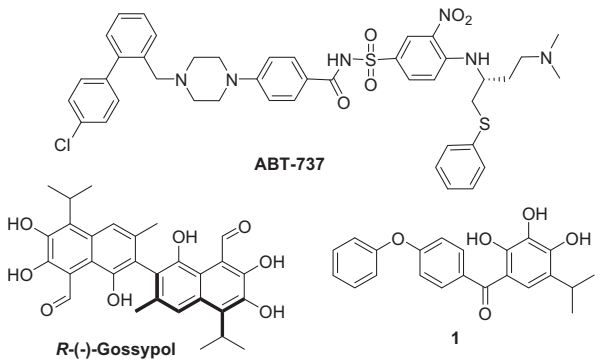

Fig. 1. Selected inhibitors of Bcl-2 and/or BcL-xL proteins.

* Corresponding author. Tel.: +33 (0)2 23 23 57 15; fax: +33 (0)2 23 23 69 78; e-mail address: rene.gree@univ-rennes1.fr (R. Grée).

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Polyphenol derivatives are widely used in medicinal chemistry, including for anticancer agents.[9] For instance, gossypol, which showed good activities towards Bcl-xL, Bcl-2, and Mcl-1 has entered into clinical trials,[10] and various analogues of gossypol have been designed.[11] The derivative **1** demonstrated good activities against Bcl-2 and Mcl-1.[11d] It induced apoptosis and cell death as a single agent in several cancer cell lines. Later developments showed that the activity can be improved by changing the isopropyl group of **1** into more bulky groups.[11d] Molecular docking studies reported in the literature gave strong indications that for these series of molecules, the different phenolic OH groups and the benzophenone carbonyl have important interactions with the amino acids inside the binding pockets of the antiapoptotic proteins.[11] Further, recent results have established that other analogues, based on TW-37 and derivatives, exhibit very promising properties against Mcl-1.[12]

As part of our program towards new anticancer molecules,[13] we reported recently a preliminary structure–activity relationship study on selected polyphenol derived molecules. We have first shown that **1** was able to act as Bcl-xL inhibitor. Then, we have demonstrated that the use of a *p*-fluorobenzyl group to replace the isopropyl substituent in position 5 resulted in an increase of activity (Fig. 2, compound **A2**). Finally we have established that the phenol at position 3 had a key role regarding disruption of Bax/Bcl-xL interaction.[14,15] In continuation of these studies, it appeared interesting to explore the possibility of replacing the central aromatic ring by either five-membered or six-membered heteroaromatic systems. In this publication we will describe the synthesis of representative examples in the two series: the triazole analogues (for series B) and several heteroaromatic compounds (pyrimidines, pyrimidone, and pyridine for series C). We investigated their ability to inhibit Bax/Bcl-xL interaction, using a previously reported Bioluminescence Resonance Energy Transfer (BRET) assay in whole live cells.[14] We wanted to analyze if the new polyphenol derivatives retained the ability of gossypol to interfere with the BH3 binding activity of antiapoptotic Bcl-xL protein and because disruption of this interaction is critical to promote cell death.[7] Finally, we will briefly analyze our results by using molecular docking studies.

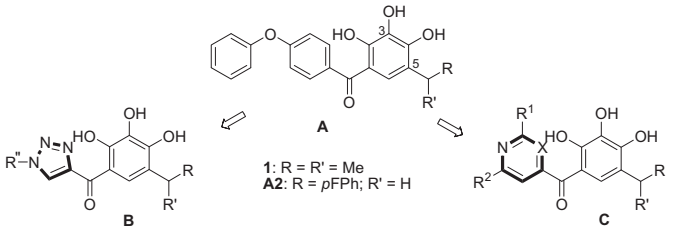
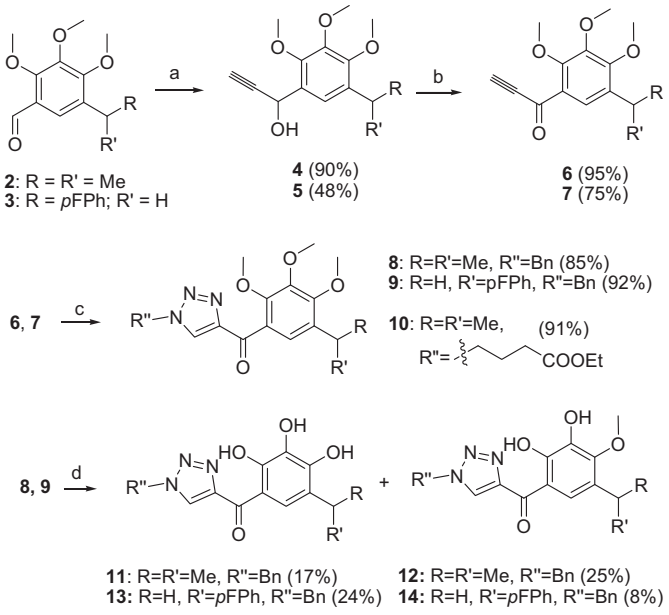


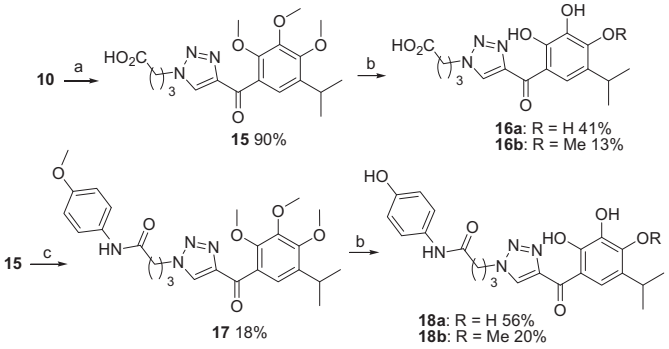
Fig. 2. Design of our target molecules.

2. Results and discussions

The synthesis of the triazoles is based on the use of the 'click chemistry',[16] as described in Schemes 1 and 2. The key intermediates are the propargylic ketones **6** and **7**, easily prepared in two steps and 85% and 36% yield, respectively, from the known aldehydes **2** and **3**.[14] Then, reaction with benzyl azide under copper catalysis gave the desired triazoles **8** and **9**. A final deprotection step afforded mixtures of fully deprotected derivatives **11** and **13** with monoprotected compounds **12** and **14**, separated by silica gel chromatography. For the latter molecules, the position of the remaining methoxy group, in para position to the carbonyl substituent, was established by extensive NMR studies.



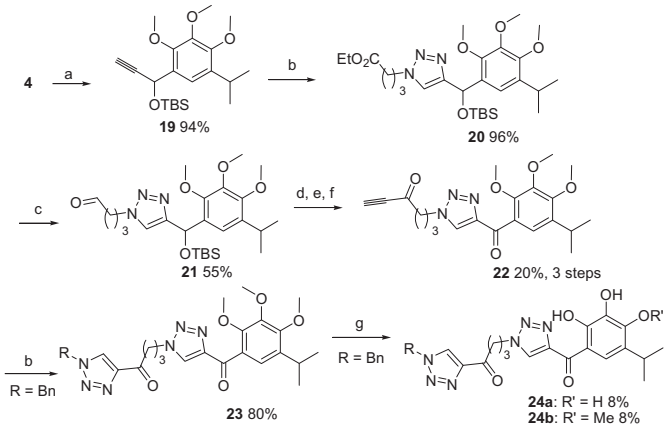
Scheme 1. Synthesis of the first series of triazoles derivatives. Reagents and conditions: (a) ethynylmagnesiumbromide, THF, 0 °C–rt; (b) IBX, DMSO/$CHCl_3$ 1/1, 80 °C; (c) R″N_3, $CuSO_4$, Na ascorbate, $CHCl_3$, reflux; (d) BBr_3, DCM, −78 °C–rt.



Scheme 2. Synthesis of the second series of triazoles **16** and **18**. Reagents and conditions: (a) LiOH, MeOH, 50 °C; (b) BBr_3, DCM, −78 °C–rt; (c) *p*-MeOPhNH_2, DCC, DMAP, DCM, rt.

To explore possible polar interactions inside the binding pockets of the Bcl-xL protein, it appeared of interest to introduce functional polar groups on the R″ chain. Therefore, the reaction of **6** with a ω-functionalized azide was performed to give the triazole **10**. Saponification gave acid **15** and, after deprotection, a mixture of **16a** and **16b** separated by chromatography. On the other hand coupling with *p*-methoxyaniline gave amide **17** and, after deprotection, the polyphenols targets **18a** and **18b** were separated by chromatography.

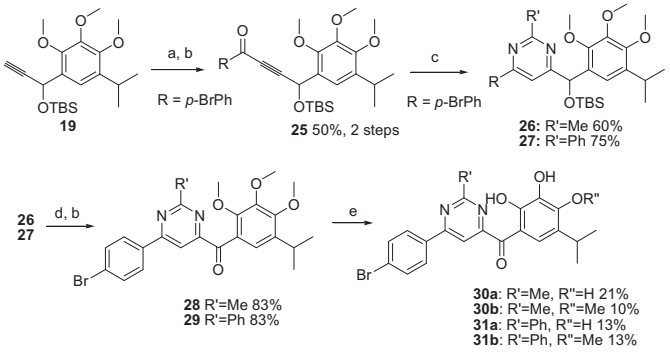
Based on literature data on the use of bistriazoles as peptidomimetics,[17] it appeared interesting to prepare also some bistriazoles derivatives of this type and this has been performed following the route indicated in Scheme 3. Protection of the propargylic alcohol **4** gave TBS ether **19**, which was subjected to the addition of the ω-functionalized azide affording triazole **20**.



Scheme 3. Synthesis of the bistriazoles derivatives **24**. Reagents and conditions: (a) TBSCl, Im, DMAP, DCM, rt; (b) RN_3, $CuSO_4$, Na ascorbate, acetone, reflux; (c) DIBAL-H, THF, −78 °C; (d) ethynylmagnesiumbromide, THF, 0 °C–rt; (e) TBAF, THF, rt; (f) IBX, DMSO/$CHCl_3$ 1/1, 80 °C; (g) BBr_3, DCM, −78 °C–rt.

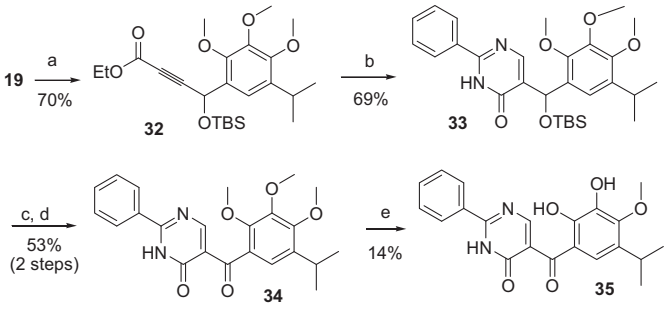
Dibal-H mediated reduction gave the aldehyde **21**, which was transformed, via the same two-step sequence, into the propargylic ketone **22**. This relatively unstable intermediate was used directly for the next step where addition of benzyl azide gave the bis triazole **23**. Deprotection gave a mixture of the target molecules **24a** and **24b**, however in poor yields (8% each, after separation by chromatography).

The synthesis of the pyrimidines takes also advantage of the chemistry of propargylic ketones, as indicated in Scheme 4. Metalation of propargylic ether **19**, followed by trapping with *p*Br-benzaldehyde and oxidation with IBX, gave the key intermediate **25**. Then, reaction with acetamidine or benzamidine afforded the desired pyrimidines **26** and **27** in 60% and 75% yield, respectively. A TBAF-mediated deprotection, followed by oxidation with IBX, gave the ketones **28** and **29** in 83% overall yield. A final deprotection step using BBr_3 afforded the target molecules, again as mixtures of the fully deprotected derivatives **30a** and **31a** with the monoprotected analogues **30b** and **31b**, separated by chromatography.



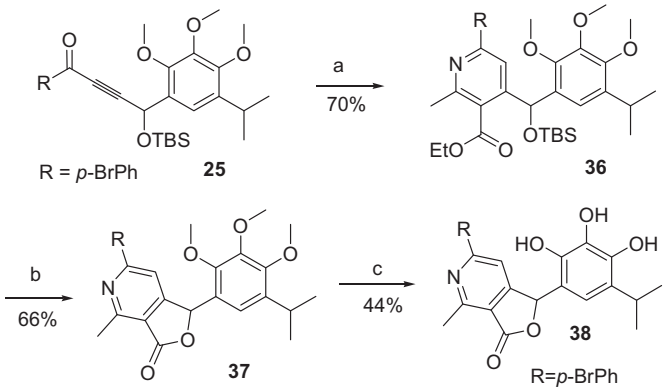
Scheme 4. Synthesis of the pyrimidines **30** and **31**. Reagents and conditions: (a) *t*-BuLi, Et_2O, −78 °C then RCHO, −78 °C–rt; (b) IBX, DMSO/$CHCl_3$ 1/1, 80 °C; (c) amidine derivatives, Na_2CO_3, CH_3CN, reflux; (d) TBAF, THF, rt; (e) BBr_3, DCM, −78 °C–rt.

A pyrimidone[18] was also prepared by the route indicated in Scheme 5. The ester **32** was prepared in 70% yield from **19** by metalation and trapping with ethyl chloroformate. Then, reaction with benzamidine gave the pyrimidone **33** in 69% yield. Starting from **33**, the same sequence of reactions as described for the pyrimidines afforded the ketone **34**. The final deprotection proved to be difficult and only the monoprotected derivative **35** could be obtained, albeit in low yield (14% after chromatography).



Scheme 5. Synthesis of the pyrimidone **35**. Reagents and conditions: (a) *t*-BuLi, Et_2O, −78 °C then ClCOOEt, −78 °C–rt; (b) benzamidine, Na_2CO_3, CH_3CN, reflux; (c) TBAF, THF, rt; (d) IBX, DMSO/$CHCl_3$ 1/1, 80 °C; (e) BBr_3, DCM, −78 °C–rt.

A pyridine was also prepared by using the Bohlmann–Ratz reaction[19] under the conditions described by Bagley (Scheme 6).[20] Condensation of the propargylic ketone **25** with ethyl acetoacetate and ammonia with catalysis by iodine gave the pyridine **36** in 70% yield. Reaction with $BF_3{\cdot}OEt_2$ gave the lactone **37** and after a final deprotection step the target **38** was isolated in 44% yield.



Scheme 6. Synthesis of the pyridine **38**. Reagents and conditions: (a) ethyl acetoacetate, NH_4OAc, (cat) I_2, EtOH, 50 °C; (b) $BF_3{\cdot}OEt_2$, THF, 50 °C; (c) BBr_3, DCM, −78 °C–rt.

3. Results of BRET assays

The biological activity of synthesized molecules was evaluated using a BRET assay, as previously described.[14] Results for the triazoles are reported in Fig. 3. If we consider first the series

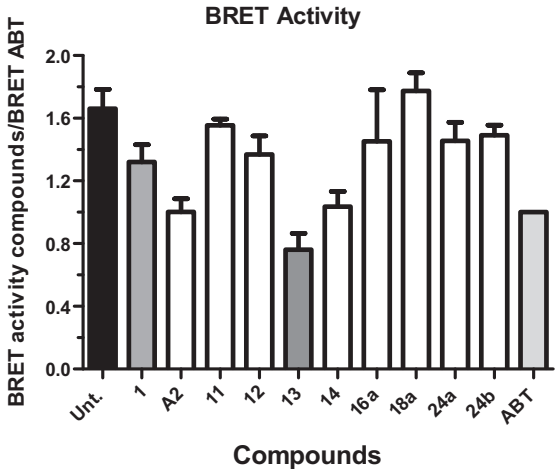


Fig. 3. BRET activity regarding disruption of Bax/Bcl-xL interaction, for the triazoles series (**Unt**: not treated).

with the ^{i}Pr chain, we see that the introduction of the triazole unit is not beneficial since compounds **11** and **12** are less active than the acylpyrogallol reference molecule **1**. Replacement of the benzyl group with more polar substituents, like in **16a** and **18a**, is leading to inactive compounds. On the other hand, the bis triazole derivatives **24a** and **24b** are also nonactive molecules. We have shown previously that replacement of the ^{i}Pr unit by a *p*-fluorobenzyl substituent improved the activity of the acylpyrogallol-type molecules affording a compound as active as the ABT 737. This proved to be true also here since the analogue bearing this side chain **13** was found to be very active: it is not only better than the acylpyrogallol **1** but also much more active than the classical reference in these series, the ABT 737. Although less potent, the monomethoxy analogue **14** is still in the same range of activity as the ABT 737.

The results for the six-membered analogues are reported in Fig. 4. Pyrimidine **30b**, pyrimidone **35**, and pyridine **38** exhibit an activity in the same range as the acylpyrogallol reference compound **1** but they are less active than the ABT 737. On the other hand **30a** and **31a** are inactive compounds.

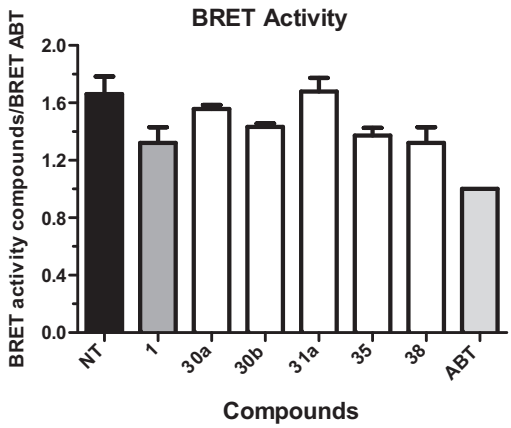


Fig. 4. BRET activity regarding disruption of Bax/Bcl-xL interaction, for the six-membered derivatives (**NT**: not treated).

Determination of the ligand-binding site resulted from a pipeline of molecular modeling protocols involving pharmacophore definition, protein flexibility analysis, and ligand docking.[21] The identified region corresponds roughly to the tetrahydro-naphtalen-1-ol's site 2, or Ile85 binding crevice of Bak peptide.[4a] Docking of the present series suggested that molecules share a common binding mode. However, the precise interacting amino acids vary between compounds. The inhibitors are always inserted in the subcavity edged by Glu96, Tyr195, Trp137, and Glu92. Glu96 often forms hydrogen bonds (HB) with the polyphenol of the ligands, and Tyr195 is often engaged in π-stacking interaction. Fig. 5A shows the predicted binding mode of reference compound **1**, forming 2 HB with Glu96, one with Arg100, and its phenolic ring stacked with Tyr195. The diphenyl-ether fills the cavity formed by Asn136, Phe191, and Trp137. The ^{i}Pr group is relatively solvent-exposed. Although sharing the same chemical scaffold, reference compound **A2** undergoes a slight translation in the binding site, with a polyphenol centroïd displacement of 1.5 Å. The HB with Glu96 is conserved, but Tyr195 makes now π-stacking with the *p*-fluorophenyl, whose fluorine forms halogen bond with Glu92 (Fig. 5B). A HB is gained between the ketone and Tyr101. These novel interactions explain certainly the higher affinity of compound **A2** as compared to compound **1**.

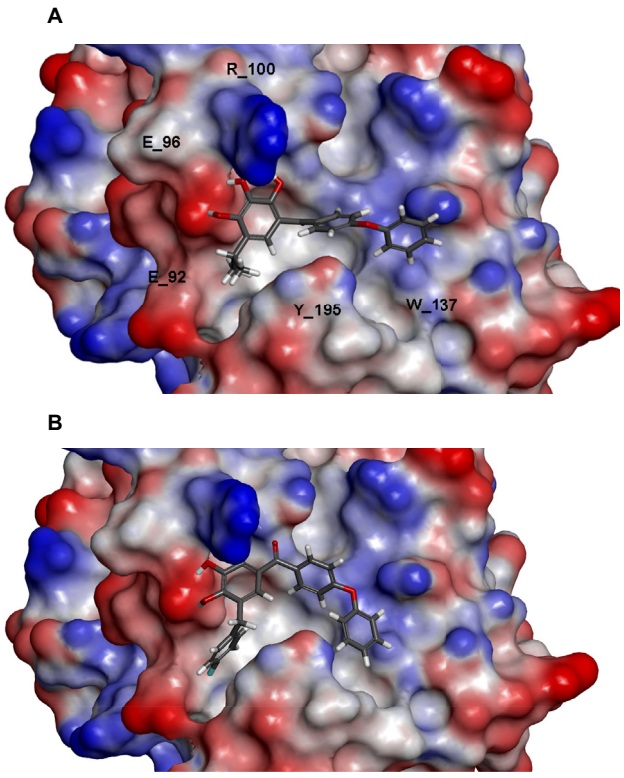


Fig. 5. (A) Docking of reference compound **1** in the Bcl-xL binding site. The protein is represented by its Connolly surface, colored according to the electrostatic potential, from red (negative) to blue (positive). (B) Putative binding mode of reference compound **A2**.

The triazoles have very similar binding mode (Fig. 6). The small increase of affinity for compound **13** versus **A2** is probably due to the reduced hydrophobicity of the molecule, in a solvent-exposed binding site (clog *P*=−0.2 for triazole vs 1.8 for phenyl). On the contrary, the polyphenol of pyrimidines can't form any HB. Burying of the ^{i}Pr in the hydrophobic cavity forced the hydroxyls to be solvent-exposed (Fig. 7A). The polyphenol of pyridine compound **38** is also away from Glu96, but the γ-butyrolactone is able to form HB with Arg100, and the bromophenol suits well to the hydrophobic cavity (Fig. 7B).

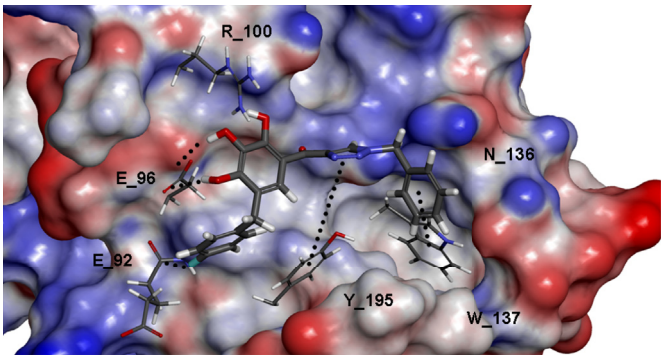


Fig. 6. Docking of triazole **13**. Key amino acids are labeled, and precise intermolecular interactions symbolized by dotted lines.

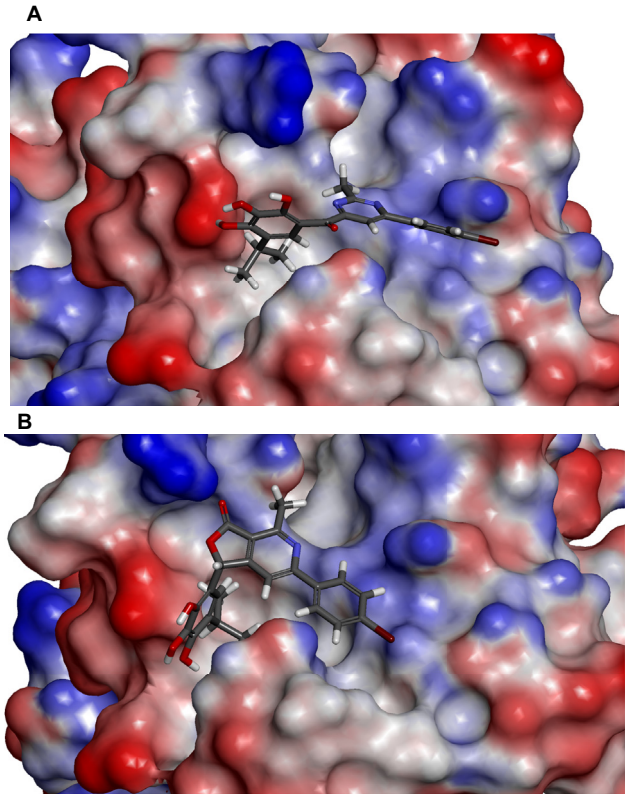


Fig. 7. (A) Predicted binding mode of pyrimidine **30a**. (B) Docking of pyridine **38**.

In conclusion, synthetic strategies based on the use of propargylic derivatives allowed efficient preparations of the mixed heteroaromatic-polyphenol target molecules. Some of these compounds (triazole, pyrimidone, pyridine) appear as attractive new structures for further design of Bax/Bcl-xL inhibitors. Especially the triazole **13**, which is more potent than ABT 737 in disrupting Bax/Bcl-xL interaction, is a promising hit for extended biological studies. Molecular docking gave a rationale for the interactions of these molecules with Bcl-xL and will be of much use for optimization of their inhibitory properties. Corresponding studies are under development in our groups and will be reported in due course.

4. Experimental section

4.1. General information

All reagents were obtained commercially and used without further purification. All reactions have been carried out under a nitrogen atmosphere and anhydrous conditions. The solvents used were freshly distilled under anhydrous conditions, unless otherwise specified. The reaction mixtures have been magnetically stirred with Teflon stirring bars, and the temperatures were measured externally. Reactions that require anhydrous conditions have been carried out by using oven dried (120 °C, 24 h) glassware. Yields refer to chromatographically and spectroscopically (^{1}H and ^{13}C NMR) homogeneous materials, and the reactions have been monitored by thin layer chromatography (TLC), carried out on 0.25 mm Merck silica gel plates (60 F_{254}). The eluents used were mixtures of pentane and ethyl acetate (EA), with detection by UV light, or a *p*-anisaldehyde staining solution. Acros silica gel (60, particle size 0.040–0.063 mm) was used for column chromatography. Nuclear magnetic resonance (NMR) spectra have been recorded with Bruker Avance 400 and 300 spectrometers. ^{1}H NMR spectra: δ (H) are given in parts per million relative to tetramethylsilane (TMS), using [δ ($CHCl_3$)=7.26 ppm] as internal reference. ^{13}C NMR spectra: δ (C) are given in ppm relative to TMS, using [δ ($CDCl_3$)=77.0 ppm] as internal reference. Multiplicities were designated as singlet (s), doublet (d), triplet (t), quadruplet (q), multiplet (m) or br (broad). Mass spectral analyses have been performed at the Centre Régional de Mesures Physiques de l'Ouest (CRMPO) in Rennes (France).

4.2. Preparation of phenolic triazole-containing compounds 11–14, 16a, 16b, 18a, 18b, 24a, 24b

4.2.1. Propargylic alcohol ***4***. To a solution of aldehyde **2** (1 g, 4.2 mmol) in THF (5 ml) under nitrogen at 0 °C was added dropwise ethynyl magnesium bromide (8.4 ml, 2 equiv, 0.5 M in THF). The reaction mixture was stirred for 2 h. The reaction mixture was quenched with a saturated ammonium chloride solution and extracted with Et_2O. The combined organic layer was dried over $MgSO_4$ and concentrated under reduced pressure. The crude product was purified on a silica gel column using a 9/1 mixture of pentane/EA as eluent to afford **4** (1 g, 90%) as a light yellow viscous oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 7.09 (s, 1H), 5.54 (dd, *J*=7.2, 2.4 Hz, 1H), 4.00 (s, 3H), 3.90 (s, 3H), 3.88 (s, 3H), 3.28 (st, *J*=6.9 Hz, 1H), 3.14 (d, *J*=7.2 Hz, 1H, OH) 2.63 (d, *J*=2.3 Hz, 1H), 1.20 (d, *J*=6.9 Hz, 6H). ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 151.5, 149.2, 146.0, 137.7, 128.8, 119.4, 84.1, 73.9, 61.4, 61.2, 61.1, 60.5, 26.9, 23.4. HRMS (EI^+): $C_{15}H_{20}O_4$ M^+ *m*/*z*, calcd 264.1362, found 264.1355.

4.2.2. Propargylic alcohol ***5***. Procedure used for compound **4** was applied for compound **5**. The reaction was performed with **3** (761 mg, 2.5 mmol), 0.5 M of ethynyl magnesium bromide solution in THF (7.5 ml, 1.5 equiv) and THF (5 ml) to afford **5** (394 mg, 48%) as a light yellow viscous oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 7.14 (dd, *J*=5.5, 8.6 Hz, 2H), 7.00 (s, 1H), 6.97 (t, *J*=8.7 Hz, 2H), 5.50 (d, *J*=1.7 Hz, 1H), 3.98 (s, 3H), 3.89 (s, 2H), 3.88 (s, 3H), 3.72 (s, 3H), 3.03 (br s, 1H), 2.61 (d, *J*=2.3 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 161.3 (d, *J*=243.7 Hz), 152.3, 150.2, 146.3, 136.4 (d, *J*=3.2 Hz), 130.1 (d, *J*=7.8 Hz), 130.0, 128.8, 123.2, 115.0 (d, *J*=21.2 Hz), 83.9, 74.0, 61.2, 61.1, 60.6, 60.5, 35.2. ^{19}F NMR (282.4 MHz, $CDCl_3$) δ (ppm): −117.5. HRMS (ESI^+): $C_{19}H_{19}O_4FNa$ $[M+Na]^+$ *m*/*z*, calcd 353.1165, found 353.1165.

4.3. General procedure 1 for oxidation with IBX, example: preparation of compound 6

4.3.1. Propargylic ketone ***6***. A solution of alcohol **4** (1.46 g, 6.2 mmol), IBX (4.66 g, 3 equiv) in a 1/1 mixture of $CHCl_3$/DMSO (10 ml) was heated under reflux for 2 h until total consumption of alcohol. After cooling down, the mixture was poured into water and filtered on Celite. The solution was then extracted with Et_2O, washed with water and brine. The combined organic layers were dried over $MgSO_4$ and concentrated under reduced pressure. The crude product was purified on a silica gel column using a 9/1 mixture pentane/ether as eluent to afford **6** (1.42 g, 95%) as a yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 7.64 (s, 1H), 3.99 (s, 3H), 3.98 (s, 3H), 3.90 (s, 3H), 3.40 (s, 1H), 3.26 (st, *J*=6.9 Hz, 1H), 1.23 (d, *J*=6.9 Hz, 6H). ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 175.1, 156.8, 153.6, 146.1, 137.6, 125.9, 123.8, 82.5, 78.9, 61.5, 61.1, 60.7, 27.0, 23.0. HRMS (EI^+): $C_{15}H_{28}O_4$ M^+. *m*/*z*, calcd 262.1205, found 262.1202.

4.3.2. Propargylic ketone ***7***. According to general procedure 1, the reaction was performed with **5** (374 mg, 1.13 mmol), IBX (476 mg, 1.5 equiv), and a 3/1 mixture $CHCl_3$/DMSO (4 ml) to afford **7** (278 mg, 75%) as a yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 7.55 (s, 1H), 7.14 (dd, *J*=5.4, 8.7 Hz, 2H), 6.96 (t, *J*=8.7 Hz, 2H), 3.96 (s, 3H), 3.89 (s, 2H), 3.87 (s, 3H), 3.82 (s, 3H), 3.37 (s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 174.8, 161.3 (d, *J*=244.0 Hz), 157.2, 154.6,

146.3, 135.9 (d, J=3.2 Hz), 130.0 (d, J=7.8 Hz), 127.5, 125.8, 115.1 (d, J=21.2 Hz), 82.4, 79.1, 61.6, 60.8, 60.7, 35.4. ^{19}F NMR (282.4 MHz, $CDCl_3$) δ (ppm): −117.2. HRMS (ESI$^+$): $C_{19}H_{17}O_4FNa$ $[M+Na]^+$ m/z, calcd 351.1008, found 351.1009.

4.4. General procedure 2 for click chemistry, example: preparation of compound 8

*4.4.1. Triazole **8**.* A solution of propargyl ketone **6** (740 mg, 2.82 mmol), benzyl azide (413 mg, 1.1 equiv), copper (II) sulfate (36 mg, 0.05 equiv), sodium ascorbate (282 μl, 0.1 equiv, 1 M in H_2O) in $CHCl_3$ (3 ml) was stirred under reflux for 2 h. After cooling down, the mixture was added 25% NH_4OH solution and then extracted with ethyl acetate. The combined organic phases were dried over $MgSO_4$ and concentrated in vacuo. The product was purified on a silica gel column with a 7/3 mixture of pentane/AcOEt as eluent to afford **8** (950 mg, 85%) as a white solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 8.06 (s, 1H), 7.42–7.30 (m, 5H), 7.23 (s, 1H), 5.59 (s, 2H), 3.94 (s, 3H), 3.89 (s, 3H), 3.82 (s, 3H), 3.26 (st, J=6.9 Hz, 1H), 1.22 (d, J=6.9 Hz, 6H). ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 187.2, 154.7, 151.1, 148.7, 145.9, 137.3, 133.8, 129.3, 129.1, 128.3, 127.8, 127.1, 122.3, 61.8, 61.1, 60.6, 54.4, 27.0, 23.2. HRMS (ESI$^+$): $C_{22}H_{25}N_3O_4Na$ $[M+Na]^+$ m/z, calcd 418.1743, found 418.1742.

*4.4.2. Triazole **9**.* According to general procedure 2, the reaction was performed with **7** (231 mg, 0.7 mmol), $CuSO_4\cdot 5H_2O$ (8.75 mg, 0.05 equiv), 1 M sodium ascorbate solution (70 μl, 0.1 equiv), benzyl azide (140.5 mg, 1.5 equiv), and $CHCl_3$ (4 ml) to afford **9** (297 mg, 92%) as a white solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 8.03 (s, 1H), 7.43–7.37 (m, 3H), 7.34–7.27 (m, 2H), 7.18–7.12 (m, 3H), 6.93 (d, J=8.7 Hz, 2H), 5.58 (s, 2H), 3.90 (s, 2H), 3.86 (s, 3H), 3.84 (s, 3H), 3.78 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 186.7, 161.3 (d, J=243.7 Hz), 155.1, 152.1, 148.5, 146.2, 136.2 (d, J=3.2 Hz), 133.7, 130.2 (d, J=7.8 Hz), 129.6, 129.3, 129.1, 128.3, 127.6, 127.0, 125.9, 115.0 (d, J=21.2 Hz), 61.8, 60.7, 60.6, 54.4, 35.3. ^{19}F NMR (282.4 MHz, $CDCl_3$) δ (ppm): −117.5. HRMS (ESI$^+$): $C_{26}H_{24}N_3O_4Na$ $[M+Na]^+$ m/z, calcd 484.1643, found 484.1646.

*4.4.3. Triazole **10**.* According to general procedure 2, the reaction was performed with **6** (660 mg, 2.52 mmol), $CuSO_4\cdot 5H_2O$ (31.5 mg, 0.05 equiv), 1 M sodium ascorbate solution (252 μl, 0.1 equiv), azide (435 mg, 1.1 equiv), and $CHCl_3$ (3 ml) to afford **10** (987 mg, 91%) as a colorless viscous oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 8.17 (s, 1H), 7.23 (s, 1H), 4.52 (t, J=6.9 Hz, 2H), 4.14 (q, J=7.2 Hz, 2H), 3.94 (s, 3H), 3.89 (s, 3H), 3.83 (s, 3H), 3.26 (st, J=6.9 Hz, 1H), 2.38 (t, J=6.9 Hz, 2H), 2.28 (qn, J=6.9 Hz, 2H), 1.26 (t, J=7.2 Hz, 3H), 1.21 (d, J=6.9 Hz, 6H). ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 187.1, 172.1, 154.6, 151.1, 148.4, 145.9, 137.3, 127.9, 127.4, 122.3, 61.8, 61.1, 60.8, 60.6, 49.5, 30.5, 27.0, 25.3, 23.2, 14.2. HRMS (ESI$^+$): $C_{21}H_{29}N_3O_6Na$ $[M+Na]^+$ m/z, calcd 442.1954, found 442.1953.

4.5. General procedure 3 for demethylation with BBr_3, example: preparation of compounds 11 and 12

To a solution of compound **8** (178 mg, 0.45 mmol) was added dropwise BBr_3 (5.4 ml, 12 equiv, 1 M in CH_2Cl_2) in CH_2Cl_2 (4 ml) at −78 °C under nitrogen. The reaction mixture was allowed to come back to rt and stirred for 6 h in dark. The mixture was then cooled again to 0 °C and after addition of water, it was diluted with CH_2Cl_2, stirred for 1 h before extraction with CH_2Cl_2. The combined organic layers were dried over $MgSO_4$ and concentrated under reduced pressure. The crude product was purified on a silica gel column using a 7/3 mixture pentane/EA as eluent to afford polyphenolic compounds **11** (40 mg, 25%) and **12** (28 mg, 17%) as yellow solids.

*4.5.1. Triazole **11**.* ^{1}H NMR (300 MHz, acetone-d_6) δ (ppm): 12.93 (s, 1H), 8.76 (s, 1H), 8.71 (s, 1H), 8.52 (s, 1H), 8.02 (s, 1H), 7.35–7.23 (m, 5H), 5.79 (s, 2H), 3.29 (st, J=6.9 Hz, 1H), 1.27 (d, J=6.9 Hz, 6H). ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 188.4, 152.6, 151.3, 149.1, 136.3, 132.2, 130.2, 129.8, 129.4, 129.2, 127.8, 123.2, 112.9, 54.6, 27.8, 23.0. HRMS (ESI$^+$): $C_{19}H_{19}N_3O_4Na$ $[M+Na]^+$ m/z, calcd 376.1273, found 376.1261.

*4.5.2. Triazole **12**.* ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 12.70 (s, 1H), 8.65 (s, 1H), 8.15 (s, 1H), 7.48–7.33 (m, 5H), 5.61 (s, 2H), 5.57 (br s, 1H), 4.04 (s, 3H), 3.25 (st, J=6.9 Hz, 1H), 1.25 (d, J=6.9 Hz, 6H). ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 187.8, 151.0, 150.8, 148.4, 136.6, 133.5, 133.2, 129.4, 129.2, 128.5, 128.4, 121.6, 114.5, 60.6, 54.5, 27.2, 23.3. HRMS (ESI$^+$): $C_{20}H_{21}N_3O_4Na$ $[M+Na]^+$ m/z, calcd 390.1430, found 390.1433.

*4.5.3. Triazole **13**.* According to general procedure 3, the reaction was performed with **9** (270 mg, 0.59 mmol), 1 M of BBr_3 solution in DCM (5.9 ml, 10 equiv) and DCM (10 ml) to afford **13** (60 mg, 24%) and **14** (20 mg, 8%) as yellow solids. ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 12.81 (br s, 1H), 8.50 (s, 1H), 8.07 (s, 1H), 7.36–7.26 (m, 5H), 7.18 (dd, J=5.4, 8.8 Hz, 2H), 6.88 (t, J=8.7 Hz, 2H), 5.55 (s, 2H), 3.91 (s, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 187.2, 161.1 (d, J=244.0 Hz), 152.0, 150.3, 148.3, 136.5 (d, J=3.2 Hz), 133.6, 131.3, 129.9 (d, J=7.8 Hz), 129.2, 129.1, 128.2, 128.1, 126.4, 119.8, 114.9 (d, J=21.3 Hz), 114.6, 112.3, 54.3, 34.8. ^{19}F NMR (282.4 MHz, $CDCl_3$) δ (ppm): −117.4. HRMS (ESI$^+$): $C_{23}H_{18}N_3O_4FNa$ $[M+Na]^+$ m/z, calcd 442.1179, found 442.1177.

*4.5.4. Triazole **14**.* ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 12.82 (s, 1H), 8.60 (s, 1H), 8.12 (s, 1H), 7.42–7.33 (m, 5H), 7.19 (dd, J=5.4, 8.8 Hz, 2H), 6.94 (t, J=8.7 Hz, 2H), 5.60 (s, 2H), 5.59 (br s, 1H), 3.93 (s, 2H), 3.88 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 187.6, 161.3 (d, J=244.0 Hz), 152.0, 151.0, 148.3, 136.8 (d, J=3.2 Hz), 136.7, 133.5, 130.0 (d, J=7.8 Hz), 129.4, 129.3, 128.5, 128.4, 125.5, 125.2, 114.9 (d, J=21.3 Hz), 114.2, 60.3, 54.5, 35.7. ^{19}F NMR (282.4 MHz, $CDCl_3$) δ (ppm): −117.3. HRMS (ESI$^+$): $C_{24}H_{20}N_3O_4FNa$ $[M+Na]^+$ m/z, calcd 456.1336, found 456.1334.

*4.5.5. Triazole **15**.* A solution of triazole **10** (306 mg, 0.73 mmol) with LiOH (61.3 mg, 2 equiv) in MeOH (2 ml) was stirred at 40 °C for 1 h. After cooling down to rt, the mixture was neutralized with a 10% HCl solution, and then extracted with EA. The combined organic layers were dried over $MgSO_4$ and concentrated under reduced pressure to give triazole acid **15** (257 mg, 90%) as a white solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 9.06 (br s, 1H), 8.21 (s, 1H), 7.23 (s, 1H), 4.54 (t, J=6.9 Hz, 2H), 3.93 (s, 3H), 3.88 (s, 3H), 3.82 (s, 3H), 3.26 (st, J=6.9 Hz, 1H), 2.44 (qn, J=6.9 Hz, 2H), 2.29 (t, J=6.9 Hz, 2H), 1.20 (d, J=6.9 Hz, 6H). ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 187.1, 177.1, 154.8, 151.1, 148.3, 145.9, 137.5, 127.8, 127.6, 122.3, 61.9, 61.2, 60.7, 49.4, 30.2, 27.0, 25.1, 23.3. HRMS (ESI$^+$): $C_{19}H_{25}N_3O_6Na$ $[M+Na]^+$ m/z, calcd 414.1641, found 414.1638.

*4.5.6. Triazole **16a**.* According to general procedure 3, the reaction was performed with **15** (60 mg, 0.15 mmol), 1 M of BBr_3 solution in DCM (2.0 ml, 13.3 equiv) and DCM (3 ml). A purification on silica gel (eluent: pentane/EA 7/3) afford **16a** (22 mg, 41%) and **16b** (7 mg, 13%) as yellow solids. ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 12.85 (s, 1H), 8.70 (s, 1H), 8.26 (s, 1H), 6.15 (br s, 1H), 5.62 (br s, 1H), 4.55 (m, J=6.7 Hz, 2H), 3.24 (m, J=6.9 Hz, 1H), 2.46–2.26 (m, 4H), 1.29 (d, J=6.9 Hz, 6H). ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 187.4, 172.6, 150.2, 148.7, 148.4, 130.4, 128.6, 127.3, 123.0, 112.5, 51.9, 49.5, 30.3, 27.2, 25.3, 22.5. HRMS (ESI$^+$): $C_{16}H_{19}N_3O_6Na$ $[M+Na]^+$ m/z, calcd 372.1172, found 372.1170.

*4.5.7. Triazole **16b**.* ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 12.75 (s, 1H), 8.66 (s, 1H), 8.27 (s, 1H), 5.61 (br s, 1H), 4.55 (t, J=6.7 Hz, 2H), 4.05 (s, 3H), 3.25 (st, J=6.9 Hz, 1H), 2.47–2.24 (m, 4H), 1.26 (d,

J=6.9 Hz, 6H). ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 187.8, 172.5, 151.0, 150.8, 148.3, 136.6, 133.2, 128.7, 121.6, 114.6, 60.6, 51.9, 49.6, 30.3, 27.3, 25.3, 23.3. HRMS (ESI$^+$): $C_{17}H_{21}N_3O_6Na$ [M+Na]$^+$ m/z, calcd 386.1328, found 386.1328.

4.5.8. Triazole ***17***. A solution of triazole acid **15** (237 mg, 0.61 mmol), DCC (138 mg, 1.1 equiv), DMAP (4.7 mg, 0.06 equiv) in CH_2Cl_2 (3 ml) was stirred for 15 min at rt. To the mixture was then added *p*-methoxyaniline (113 mg, 1.5 equiv) and it was stirred overnight at rt. The mixture was then concentrated under reduced pressure and purified on a silica gel column to afford triazole amide **17** (55 mg, 18%) as a light yellow viscous oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 8.18 (s, 1H), 8.00 (s, 1H), 7.37 (d, J=9.0 Hz, 2H), 7.19 (s, 1H), 6.80 (d, J=9.0 Hz, 2H), 4.54 (t, J=6.2 Hz, 2H), 3.92 (s, 3H), 3.86 (s, 3H), 3.79 (s, 3H), 3.75 (s, 3H), 3.24 (st, J=6.9 Hz, 1H), 2.39–2.26 (m, 4H), 1.18 (d, J=6.9 Hz, 6H). ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 186.9, 169.5, 156.3, 154.6, 150.9, 148.1, 145.9, 137.5, 130.8, 127.9, 127.8, 122.1, 121.8, 114.0, 61.9, 61.0, 60.6, 55.4, 49.5, 33.0, 27.0, 25.9, 23.2. HRMS (ESI$^+$): $C_{26}H_{32}N_4O_6Na$ [M+Na]$^+$ m/z, calcd 519.2219, found 519.2220.

4.5.9. Triazole ***18a***. According to general procedure 3, the reaction was performed with **17** (34.5 mg, 0.07 mmol), 1 M of BBr_3 solution in DCM (1.12 ml, 16 equiv) and DCM (3 ml). A purification by HPLC on a reverse column using gradient mixture of ACN/H_2O as eluent afford **18a** (16 mg, 56%) and **18b** (6 mg, 20%) as yellow solids. ^{1}H NMR (300 MHz, acetone-d_6) δ (ppm): 12.99 (br s, 1H), 9.01 (br s, 1H), 8.79 (s, 1H), 8.72 (s, 1H), 7.45 (d, J=8.8 Hz, 2H), 6.75 (d, J=8.8 Hz, 2H), 4.66 (t, J=6.6 Hz, 2H), 3.28 (st, J=6.9 Hz, 1H), 2.48–2.29 (m, 4H), 1.27 (d, J=6.9 Hz, 6H). ^{13}C NMR (75 MHz, acetone-d_6) δ (ppm): 188.5, 172.0, 170.0, 154.3, 151.3, 148.8, 132.4, 132.3, 130.5, 127.8, 123.1, 121.8, 121.7, 115.9, 112.9, 50.5, 33.7, 27.8, 26.6, 23.3, 23.0. HRMS (ESI$^+$): $C_{23}H_{26}N_4O_6Na$ [M+Na]$^+$ m/z, calcd 477.1750, found 477.1752.

4.5.10. Triazole ***18b***. ^{1}H NMR (300 MHz, acetone-d_6) δ (ppm): 12.84 (s, 1H), 8.99 (br s, 1H), 8.78 (s, 1H), 8.76 (s, 1H), 8.15 (br s, 1H), 7.80 (br s, 1H), 7.45 (d, J=8.8 Hz, 2H), 6.75 (d, J=8.8 Hz, 2H), 4.67 (t, J=6.5 Hz, 2H), 4.03 (s, 3H), 3.25 (st, J=6.9 Hz, 1H), 2.48–2.30 (m, 4H), 1.24 (d, J=6.9 Hz, 6H). ^{13}C NMR (75 MHz, acetone-d_6) δ (ppm): 189.2, 170.0, 154.3, 153.1, 152.3, 149.0, 148.6, 1333, 132.5, 130.9, 121.8, 121.7, 121.6, 115.9, 115.8, 115.5, 60.7, 50.6, 33.7, 27.9, 26.6, 23.7. HRMS (ESI$^+$): $C_{22}H_{24}N_4O_6Na$ [M+Na]$^+$ m/z, calcd 463.1594, found 463.1592.

4.5.11. Triazole ***19***. A solution of propargyl alcohol **4** (1.22 g, 4.62 mmol), TBSCl (834.4 mg, 1.2 equiv), imidazole (440 mg, 1.4 equiv), and DMAP (789 mg, 1.4 equiv) in CH_2Cl_2 (3 ml) was stirred for overnight under nitrogen at rt. To the reaction mixture was then added a saturated ammonium chloride solution and it was extracted with CH_2Cl_2. The combined organic layers were dried over Mg_2SO_4 and concentrated under reduced pressure. The crude product was purified on a silica gel column using a 95/5 mixture pentane/ether as eluent to afford **19** (1.64 g, 94%) as a colorless viscous oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 7.24 (s, 1H), 5.73 (d, J=2.3 Hz, 1H), 3.92 (s, 3H), 3.90 (s, 3H), 3.87 (s, 3H), 3.27 (st, J=6.9 Hz, 1H), 2.49 (d, J=2.2 Hz, 1H), 1.22 (d, J=6.9 Hz, 3H), 1.20 (d, J=6.9 Hz, 3H), 0.93 (s, 9H), 0.18 (s, 3H), 0.11 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 150.8, 148.0, 145.5, 137.4, 130.1, 118.5, 85.5, 72.2, 61.1, 60.9, 60.5, 59.3, 26.7, 25.8, 23.6, 23.5, 18.3, −4.9. HRMS (ESI$^+$): $C_{21}H_{34}O_4SiNa$ [M+Na]$^+$ m/z, calcd 401.2124, found 401.2124.

4.5.12. Triazole ***20***. According to general procedure 2, the reaction was performed with **19** (343 mg, 0.91 mmol), $CuSO_4 \cdot 5H_2O$ (11.4 mg, 0.05 equiv), 1 M sodium ascorbate solution (91 μl, 0.1 equiv), azide derivative (270 mg, 1.9 equiv), and acetone (2 ml) to afford **20** (464 mg, 96%) as a white solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 7.30 (s, 1H), 7.13 (s, 1H), 6.24 (s, 1H), 4.36 (t, J=6.9 Hz, 2H), 4.12 (q, J=7.2 Hz, 2H), 3.86 (s, 3H), 3.84 (s, 3H), 3.75 (s, 3H), 3.24 (m, J=6.9 Hz, 1H), 2.30 (t, J=6.9 Hz, 2H), 2.18 (m, J=6.9 Hz, 2H), 1.23 (t, J=7.2 Hz, 3H), 1.17 (d, J=6.9 Hz, 3H), 1.16 (d, J=6.9 Hz, 3H), 0.87 (s, 9H), 0.02 (s, 3H), 0.01 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 172.4, 152.8, 150.4, 148.2, 145.6, 137.3, 131.8, 121.1, 118.6, 61.1, 60.9, 60.6, 60.5, 49.0, 30.6, 26.7, 25.8, 25.5, 23.6, 23.5, 18.2, 14.2, −4.9, −5.0. HRMS (ESI$^+$): $C_{27}H_{45}N_3O_6SiNa$ [M+Na]$^+$ m/z, calcd 558.2975, found 558.2972.

4.5.13. Triazole ***21***. To a solution of triazole ester **20** (416 mg, 0.78 mmol) in DCM (3 ml) at −78 °C under nitrogen, was added dropwise a 1 M DIBAL solution in hexane (0.78 ml, 1 equiv). The reaction mixture was stirred and warmed up from −78 °C to −40 °C for 2 h and 30 min. This mixture was quenched, at rt, with a 1 M sodium tartrate solution and stirred for 30 min and then it was extracted with DCM. The organic phase was concentrated in vacuo and the product was purified on a silica gel column with a 7/3 mixture of pentane/AcOEt as eluent to afford **21** (210 mg, 55%) as a colorless viscous oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 9.75 (s, 1H), 7.31 (s, 1H), 7.15 (s, 1H), 6.27 (s, 1H), 4.36 (t, J=6.9 Hz, 2H), 3.89 (s, 3H), 3.87 (s, 3H), 3.79 (s, 3H), 3.27 (st, J=6.9 Hz, 1H), 2.54 (t, J=6.9 Hz, 2H), 2.21 (qn, J=6.9 Hz, 2H), 1.21 (d, J=6.9 Hz, 3H), 1.19 (d, J=6.9 Hz, 3H), 0.91 (s, 9H), 0.05 (s, 3H), 0.04 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 200.5, 153.0, 150.4, 148.2, 145.6, 137.3, 131.8, 121.1, 118.6, 64.8, 61.1, 61.0, 60.5, 48.9, 40.3, 26.7, 25.8, 23.7, 23.6, 22.7, 18.3, −4.8, −4.9. HRMS (ESI$^+$): $C_{25}H_{41}N_3O_5SiNa$ [M+Na]$^+$ m/z, calcd 514.2713, found 514.2710.

4.5.14. Triazole ***22***. Firstly procedure used for compound **4** was applied. The reaction was performed with aldehyde **21** (290 mg, 0.59 mmol), 0.5 M of ethynyl magnesium bromide solution in THF (2.4 ml, 2 equiv) and THF (7 ml) to afford alcohol intermediate (199 mg) as a colorless viscous oil. Secondly, to a solution of this alcohol (199 mg, 0.39 mmol) in THF (2 ml) at rt, was added dropwise TBAF (0.77 ml, 2 equiv, 1 M in THF). The reaction mixture was stirred at rt for 1 h and then quenched with a saturated ammonium chloride solution. Then the mixture was extracted with EA, dried over $MgSO_4$, and concentrated under reduced pressure. The residue was purified on a silica gel column chromatography using mixture pentane/EA 5/5 to afford diol intermediate (73 mg) as a colorless viscous oil. Lastly, this diol intermediate (73 mg, 0.18 mmol) was oxidized by using general procedure 1 with IBX (304 mg, 6 equiv) and the 1/1 mixture $CHCl_3$/DMSO (4 ml). Purification on silica gel (eluent: pentane/EA 7/3) afford dione **22** (48 mg, 20%, three steps) as a colorless viscous oil. This relatively labile compound was used directly for the next step. ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 8.17 (s, 1H), 7.24 (s, 1H), 4.49 (t, J=6.9 Hz, 2H), 3.94 (s, 3H), 3.89 (s, 3H), 3.84 (s, 3H), 3.28 (s, 1H), 3.26 (st, J=6.9 Hz, 1H), 2.71 (t, J=6.9 Hz, 2H), 2.31 (qn, J=6.9 Hz, 2H), 1.21 (d, J=6.9 Hz, 6H). HRMS (ESI$^+$): $C_{21}H_{25}N_3O_5Na$ [M+Na]$^+$ m/z, calcd 422.1692, found 422.1690.

4.5.15. Triazole ***23***. According to general procedure 2, the reaction was performed with **32** (48 mg, 0.12 mmol), $CuSO_4 \cdot 5H_2O$ (3 mg, 0.10 equiv), 1 M sodium ascorbate solution (24 μl, 0.2 equiv), benzyl azide derivative (31.9 mg, 2 equiv), and $CHCl_3$ (2 ml) to afford **33** (55 mg, 86%) as a white solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 8.19 (s, 1H), 7.98 (s, 1H), 7.38–7.32 (m, 3H), 7.30–7.24 (m, 2H), 7.20 (s, 1H), 5.54 (s, 1H), 4.52 (t, J=7.2 Hz, 2H), 3.91 (s, 3H), 3.86 (s, 3H), 3.80 (s, 3H), 3.24 (st, J=6.9 Hz, 1H), 3.18 (t, J=7.2 Hz, 2H), 2.37 (m, J=7.2 Hz, 2H), 1.18 (d, J=6.9 Hz, 6H). ^{13}C NMR (125 MHz, $CDCl_3$) δ (ppm): 193.1, 187.2, 154.6, 147.6, 145.9, 137.3, 133.6, 129.3, 129.2, 128.4, 128.0, 127.4, 125.6, 122.3, 61.9, 61.1, 60.6, 54.5, 49.7, 35.7, 27.0,

24.2, 23.3. HRMS (ESI^+): $C_{28}H_{32}N_6O_5Na$ $[M+Na]^+$ *m/z*, calcd 555.2332, found 555.2330.

*4.5.16. Triazole **24a**.* According to general procedure 3, the reaction was performed with **23** (53 mg, 0.1 mmol), 1 M BBr_3 solution in DCM (1.2 ml, 12 equiv) and DCM (3 ml). A purification by HPLC on a reverse column using gradient mixture of ACN/H_2O as eluent afford **24a** (4 mg, 8%) and **24b** (4 mg, 8%) as yellow solids. ^1H NMR (300 MHz, $CDCl_3$) δ (ppm): 12.80 (br s, 1H), 8.69 (s, 1H), 8.28 (s, 1H), 7.96 (s, 1H), 7.41–7.38 (m, 3H), 7.32–7.26 (m, 2H), 6.20 (br s, 1H), 5.57 (br s, 1H), 5.56 (s, 2H), 4.56 (t, *J*=7.2 Hz, 2H), 3.26–3.22 (m, 3H), 2.43 (qn, *J*=7.2 Hz, 2H), 1.29 (d, *J*=6.9 Hz, 6H). ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 193.1, 187.4, 150.1, 148.6, 148.3, 147.6, 133.4, 130.3, 129.4, 129.3, 128.5, 128.4, 127.2, 125.4, 123.1, 112.5, 54.6, 49.8, 36.7, 27.3, 24.1, 22.5. HRMS (ESI^+): $C_{25}H_{26}N_6O_5Na$ $[M+Na]^+$ *m/z*, calcd 513.1862, found 513.1860.

*4.5.17. Triazole **24b**.* ^1H NMR (300 MHz, $CDCl_3$) δ (ppm): 12.75 (br s, 1H), 8.65 (s, 1H), 8.30 (s, 1H), 7.96 (s, 1H), 7.41–7.38 (m, 3H), 7.32–7.26 (m, 2H), 5.57 (br s, 1H), 5.56 (s, 2H), 4.57 (t, *J*=7.2 Hz, 2H), 4.05 (s, 3H), 3.26–3.22 (m, 3H), 2.44 (qn, *J*=7.2 Hz, 2H), 1.25 (d, *J*=6.9 Hz, 6H). ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 193.1, 187.9, 151.0, 150.8, 148.2, 147.6, 136.6, 133.4, 133.2, 129.4, 129.3, 128.7, 128.4, 125.4, 121.7, 114.6, 60.6, 54.6, 49.8, 35.6, 27.3, 24.1, 23.3. HRMS (ESI^+): $C_{26}H_{28}N_6O_5Na$ $[M+Na]^+$ *m/z*, calcd 527.2019, found 527.2019.

4.6. Preparation of phenolic pyrimidine-containing compounds 30a, 30b, 31a, 31b

*4.6.1. Propargylic ketone **25**.* To a solution of propargyl derivative **19** (1.04 g, 2.75 mmol) in THF (10 ml) at −78 °C under argon, was added dropwise *t*-BuLi (1.78 ml, 1.1 equiv, 1.6 M in pentane). The mixture was stirred for 30 min. Then a solution of *p*-bromobenzaldehyde (560 mg, 1.1 equiv) in THF (2 ml) was added at −78 °C. The reaction mixture was allowed to warm up slowly to rt and stirred for 4 h and then quenched with a saturated ammonium chloride solution. The mixture was extracted with Et_2O or EA. The combined organic layers were dried over $MgSO_4$ and concentrated under reduced pressure. The crude product was purified on a silica gel column using a 9/1 mixture pentane/EA as eluent to afford the alcohol intermediate (857 mg, 55%) as a colorless viscous oil. *Alcohol intermediate*: ^1H NMR (300 MHz, $CDCl_3$) δ (ppm): 7.50–7.40 (m, 4H), 7.20 (s, 1H), 5.80 (d, *J*=2.4 Hz, 1H), 5.45 (s, 1H), 3.89 (s, 3H), 3.88 (s, 3H), 3.87 (s, 3H), 3.23 (m, *J*=6.9 Hz, 1H), 2.24 (d, *J*=2.4 Hz, 1H), 1.21 (d, *J*=6.9 Hz, 3H), 1.20 (d, *J*=6.9 Hz, 3H), 0.92 (s, 9H), 0.15 (s, 3H), 0.10 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 150.8, 148.0, 145.5, 139.6, 137.4, 131.2, 129.9, 128.4, 122.2, 118.6, 88.8, 83.1, 64.0, 61.1, 61.0, 60.5, 59.6, 26.8, 25.8, 23.6, 23.5, 18.3, −4.9. Prepared alcohol intermediate (857 mg, 1.52 mmol) was oxidized by using general procedure 1 with IBX (1.28 g, 3 equiv) and a 1/1 mixture $CHCl_3$/DMSO (4 ml) to afford **25** (770 mg, 90%) as a yellow oil. ^1H NMR (300 MHz, $CDCl_3$) δ (ppm): 7.99 (d, *J*=8.7 Hz, 2H), 7.60 (d, *J*=8.7 Hz, 2H), 7.22 (s, 1H), 5.94 (s, 1H), 3.95 (s, 3H), 3.90 (s, 3H), 3.88 (s, 3H), 3.28 (st, *J*=6.9 Hz, 1H), 1.21 (d, *J*=6.9 Hz, 3H), 1.20 (d, *J*=6.9 Hz, 3H), 0.95 (s, 9H), 0.21 (s, 3H), 0.12 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 176.7, 151.3, 148.1, 145.6, 137.7, 135.6, 131.9, 131.0, 129.5, 128.2, 118.6, 96.1, 81.3, 61.1, 61.0, 60.5, 59.8, 26.8, 25.7, 23.6, 23.5, 18.3, −4.7, −5.0. HRMS (ESI^+): $C_{28}H_{37}O_5BrSiNa$ $[M+Na]^+$ *m/z*, calcd 583.1491, found 583.1496.

*4.6.2. Pyrimidine **26**.* To a solution of propargylic ketone **25** (172 mg, 0.31 mmol) in CH_3CN (2 ml) were added sodium carbonate (78.4 mg, 2.4 equiv) and acetamidine hydrochloride (35 mg, 1.2 equiv). The solution was stirred under reflux for 1.5 h. After cooling down to rt, the mixture was filtered and concentrated in vacuo. The product was purified on a silica gel column with a 8/2 mixture of pentane/AcOEt as eluent to afford pyrimidine **26** (110 mg, 60%) as a colorless viscous oil. ^1H NMR (300 MHz, $CDCl_3$) δ (ppm): 7.96 (d, *J*=8.7 Hz, 2H), 7.81 (s, 1H), 7.64 (d, *J*=8.7 Hz, 2H), 7.03 (s, 1H), 6.07 (s, 1H), 3.89 (s, 3H), 3.87 (s, 3H), 3.86 (s, 3H), 3.24 (st, *J*=6.9 Hz, 1H), 2.72 (s, 3H), 1.20 (d, *J*=6.9 Hz, 3H), 1.14 (d, *J*=6.9 Hz, 3H), 0.94 (s, 9H), 0.07 (s, 3H), −0.03 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 173.7, 167.5, 163.1, 150.8, 149.0, 145.8, 137.3, 136.6, 132.1, 128.7, 125.1, 119.4, 109.6, 72.0, 61.1, 61.0, 60.5, 26.9, 26.2, 25.8, 23.6, 23.5, 18.2, −4.9, −5.0. HRMS (ESI^+): $C_{30}H_{41}N_2O_4BrSiNa$ $[M+Na]^+$ *m/z*, calcd 623.1917, found 623.1921.

*4.6.3. Pyrimidine **27**.* Procedure used for compound **26** was applied for compound **27**. The reaction was performed with **25** (110 mg, 0.2 mmol), benzamidine hydrochloride (37.6 mg, 1.2 equiv), Na_2CO_3 (50.9 mg, 2.4 equiv), and CH_3CN (2 ml) to afford **27** (98 mg, 75.4%) as a colorless viscous oil. ^1H NMR (300 MHz, $CDCl_3$) δ (ppm): 8.58–8.50 (m, 2H), 8.11 (d, *J*=8.6 Hz, 2H), 7.89 (s, 1H), 7.68 (d, *J*=8.6 Hz, 2H), 7.51–7.44 (m, 3H), 7.06 (s, 1H), 6.22 (s, 1H), 3.92 (s, 3H), 3.90 (s, 3H), 3.86 (s, 3H), 3.23 (st, *J*=6.9 Hz, 1H), 1.20 (d, *J*=6.9 Hz, 3H), 1.13 (d, *J*=6.9 Hz, 3H), 0.96 (s, 9H), 0.10 (s, 3H), 0.00 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 174.0, 163.6, 163.1, 150.6, 149.0, 145.7, 137.9, 137.4, 136.6, 132.1, 131.3, 130.5, 128.7, 128.3, 125.2, 119.4, 110.2, 71.8, 61.2, 61.1, 60.5, 26.8, 25.8, 23.6, 23.5, 18.2, −4.9, −5.0. HRMS (ESI^+): $C_{35}H_{43}N_2O_4BrSiNa$ $[M+Na]^+$ *m/z*, calcd 685.2073, found 685.2074.

4.7. General procedure 4 for deprotection of OTBS to OH, example: first step for preparation of compound 28

To a solution of pyrimidine **26** (254 mg, 0.42 mmol) in THF (4 ml) was added dropwise at rt TBAF (0.84 ml, 2 equiv, 1 M in THF). The reaction mixture was stirred at rt for 1 h and then quenched with a saturated ammonium chloride solution. Then the mixture was extracted with EA, dried over $MgSO_4$, and concentrated under reduced pressure to afford the alcohol as a crude product, which was used as such for the next step.

*4.7.1. Pyrimidine **28**.* Previous alcohol prepared from general procedure 4 (0.42 mmol, expected) was oxidized by using general procedure 1 with IBX (235 mg, 2 equiv) and the 3/1 mixture $CHCl_3$/DMSO (4 ml) to afford **28** (170 mg, 83%, two steps) as a light yellow viscous oil. ^1H NMR (300 MHz, $CDCl_3$) δ (ppm): 8.07 (d, *J*=8.7 Hz, 2H), 7.89 (s, 1H), 7.65 (d, *J*=8.7 Hz, 2H), 7.40 (s, 1H), 3.98 (s, 3H), 3.82 (s, 3H), 3.61 (s, 3H), 3.27 (st, *J*=6.9 Hz, 1H), 2.82 (s, 3H), 1.24 (d, *J*=6.9 Hz, 6H). ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 194.2, 167.9, 164.6, 164.2, 156.4, 152.5, 145.5, 137.6, 135.5, 132.2, 128.8, 125.8, 125.4, 123.1, 110.8, 61.1, 60.9, 60.4, 27.1, 26.2, 23.2. HRMS (ESI^+): $C_{24}H_{26}N_2O_4Br$ $[M+H]^+$ *m/z*, calcd 485.1076, found 485.1071.

*4.7.2. Pyrimidine **29**.* Firstly, according to general procedure 4, the reaction was performed with pyrimidine **27** (98 mg, 0.15 mmol), 1 M TBAF solution in THF (0.165 ml, 1.1 equiv) and THF (3 ml) to afford the alcohol as a crude product used directly for the next step. Secondly, this alcohol was oxidized by using general procedure 1 with IBX (126 mg, 3 equiv) and the 1/1 mixture $CHCl_3$/DMSO (2 ml) to afford **29** (67 mg, 83%, two steps) as a light yellow viscous oil. ^1H NMR (300 MHz, $CDCl_3$) δ (ppm): 8.56–8.52 (m, 2H), 8.21 (d, *J*=8.7 Hz, 2H), 8.04 (s, 1H), 7.70 (d, *J*=8.7 Hz, 2H), 7.52–7.44 (m, 3H), 7.46 (s, 1H), 4.01 (s, 3H), 3.84 (s, 3H), 3.59 (s, 3H), 3.32 (st, *J*=6.9 Hz, 1H), 1.27 (d, *J*=6.9 Hz, 6H). ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 194.4, 164.5, 164.3, 163.9, 156.1, 152.6, 145.6, 137.5, 137.1, 135.6, 132.2, 131.1, 128.9, 128.6, 128.5, 126.0, 125.9, 123.2, 111.4, 61.3, 61.2, 60.5, 27.2,

23.3. HRMS (ESI^+): $C_{29}H_{27}N_2O_4BrNa$ $[M+Na]^+$ *m/z*, calcd 569.1052, found 569.1053.

*4.7.3. Pyrimidine **30a**.* According to general procedure 3, the reaction was performed with **28** (154 mg, 0.32 mmol), 1 M BBr_3 solution in DCM (3 ml, 9 equiv) and DCM (3 ml). A purification by HPLC on a reverse column using gradient mixture of ACN/H_2O as eluent afford **30a** (30 mg, 21%) and **30b** (14 mg, 10%) as yellow solids. ^1H NMR (400 MHz, $CDCl_3$) δ (ppm): 8.06 (d, *J*=8.7 Hz, 2H), 8.00 (s, 1H), 7.68 (d, *J*=8.7 Hz, 2H), 7.50 (s, 1H), 3.19 (st, *J*=6.9 Hz, 1H), 2.93 (s, 3H), 1.19 (d, *J*=6.9 Hz, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 194.2, 167.6, 165.2, 162.7, 150.1, 149.6, 135.1, 132.4, 130.6, 128.9, 127.1, 126.4, 123.0, 112.8, 112.1, 26.8, 25.9, 22.3. HRMS (ESI^+): $C_{21}H_{19}N_2O_4BrNa$ $[M+Na]^+$ *m/z*, calcd 465.0426, found 465.0424.

*4.7.4. Pyrimidine **30b**.* ^1H NMR (400 MHz, $CDCl_3$) δ (ppm): 8.06 (d, *J*=8.7 Hz, 2H), 8.03 (s, 1H), 7.68 (d, *J*=8.7 Hz, 2H), 7.62 (s, 1H), 4.07 (s, 3H), 3.22 (m, *J*=6.9 Hz, 1H), 2.91 (s, 3H), 1.18 (d, *J*=6.9 Hz, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 194.3, 167.7, 165.2, 162.4, 151.2, 150.6, 137.0, 135.1, 133.2, 132.4, 128.9, 126.4, 121.6, 114.3, 112.7, 60.7, 27.0, 26.0, 23.1. HRMS (ESI^+): $C_{22}H_{21}N_2O_4BrNa$ $[M+Na]^+$ *m/z*, calcd 479.0582, found 479.0581.

*4.7.5. Pyrimidine **31a**.* According to general procedure 3, the reaction was performed with **29** (65 mg, 0.12 mmol), 1 M BBr_3 solution in DCM (1.44 ml, 12 equiv) and DCM (2 ml). A purification on silica gel (eluent: pentane/EA 7/3) afford **31a** (8 mg, 13%) and **31b** (8 mg, 13%) as yellow solids. ^1H NMR (300 MHz, $CDCl_3$) δ (ppm): 12.55 (br s, 1H), 8.67–8.61 (m, 2H), 8.19 (d, *J*=8.7 Hz, 2H), 8.10 (s, 1H), 7.96 (s, 1H), 7.70 (d, *J*=8.7 Hz, 2H), 7.58–7.50 (m, 3H), 6.24 (br s, 1H), 5.67 (br s, 1H), 3.24 (st, *J*=6.9 Hz, 1H), 1.20 (d, *J*=6.9 Hz, 6H). ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 194.5, 165.0, 163.6, 163.2, 150.3, 149.2, 136.8, 135.4, 132.3, 131.4, 130.6, 128.9, 128.7, 128.5, 127.3, 126.3, 123.5, 113.4, 112.0, 26.7, 22.6. HRMS (ESI^+): $C_{26}H_{22}N_2O_4Br$ $[M+H]^+$ *m/z*, calcd 505.0763, found 505.0768.

*4.7.6. Pyrimidine **31b**.* ^1H NMR (300 MHz, $CDCl_3$) δ (ppm): 12.49 (br s, 1H), 8.68–8.61 (m, 2H), 8.19 (d, *J*=8.7 Hz, 2H), 7.91 (s, 1H), 7.70 (d, *J*=8.7 Hz, 2H), 7.58–7.49 (m, 3H), 5.70 (br s, 1H), 4.10 (s, 3H), 3.25 (st, *J*=6.9 Hz, 1H), 1.17 (d, *J*=6.9 Hz, 6H). ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 195.0, 165.1, 163.7, 163.0, 151.2, 136.8, 135.3, 133.1, 132.3, 131.5, 128.9, 128.7, 128.5, 126.4, 122.0, 113.9, 113.4, 60.8, 26.8, 23.3. HRMS (ESI^+): $C_{27}H_{24}N_2O_4Br$ $[M+H]^+$ *m/z*, calcd 519.0919, found 519.0917.

4.8. Preparation of phenolic pyrimidone-containing compound 34

*4.8.1. Propargylic ketone **32**.* To a solution of **19** (991 mg, 2.62 mmol) in Et_2O (15 ml) at −78 °C under argon, was added dropwise *t*-BuLi (1.8 ml, 2.2 equiv, 1.6 M in pentane). The mixture was stirred for 30 min and then $ClCO_2Et$ (0.3 ml, 1.2 equiv) was added dropwise at −78 °C. The reaction mixture was allowed to warm up slowly to rt and it was stirred overnight and then quenched with a saturated ammonium chloride solution. The mixture was extracted with Et_2O. The combined organic layers were dried over $MgSO_4$ and concentrated under reduced pressure. The crude product was purified on a silica gel column using the 8/2 mixture pentane/Et_2O as eluent to give the desired product **32** (840 mg, 70%). ^1H NMR (300 MHz, $CDCl_3$) δ (ppm): 7.17 (s, 1H), 5.80 (s, 1H), 4.20 (q, *J*=7.1 Hz, 2H), 3.92 (s, 3H), 3.88 (s, 3H), 3.86 (s, 3H), 3.25 (d, *J*=6.9 Hz, 1H), 1.28 (t, *J*=7.1 Hz, 3H), 0.92 (s, 9H), 0.18 (s, 3H), 0.09 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 153.6, 151.2, 148.0, 145.5, 137.5, 128.3, 118.5, 88.2, 75.7, 61.9, 61.1, 61.0, 60.5, 59.4, 26.8, 25.7, 23.5, 23.4, 18.2, 14.0, −4.7, −5.1. HRMS (ESI^+): $C_{24}H_{38}O_6SiNa$ $[M+Na]^+$ *m/z*, calcd 473.2335, found 473.2336.

*4.8.2. Pyrimidone **33**.* To a solution of propargylic ester **32** (141 mg, 0.31 mmol) in EtOH (3 ml) were added sodium carbonate (79 mg, 2.4 equiv) and benzamidine hydrochloride (58.2 mg, 1.2 equiv). The solution was stirred under reflux for 1.5 h. After cooling down to rt, the mixture was filtered and concentrated in vacuo. The product was purified on a silica gel column with a 8/2 mixture of pentane/AcOEt as eluent to afford to afford **33** (114 mg, 69%) as a colorless viscous oil. ^1H NMR (300 MHz, $CDCl_3$) δ (ppm): 13.10 (br s, 1H), 8.23–8.09 (m, 2H), 7.58–7.38 (m, 3H), 7.00 (s, 1H), 6.77 (s, 1H), 6.01 (s, 1H), 3.99 (s, 3H), 3.91 (s, 3H), 3.86 (s, 3H), 3.22 (st, *J*=6.9 Hz, 1H), 1.17 (d, *J*=6.9 Hz, 3H), 1.13 (d, *J*=6.9 Hz, 3H), 0.92 (s, 9H), 0.10 (s, 3H), −0.07 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 171.8, 166.2, 156.1, 150.6, 149.0, 145.5, 137.5, 132.2, 131.7, 130.7, 128.8, 127.8, 119.6, 107.8, 70.5, 61.3, 61.1, 60.5, 26.8, 25.8, 23.5, 23.4, 18.2, −5.0, −5.1. HRMS (ESI^+): $C_{29}H_{40}N_2O_5SiNa$ $[M+Na]^+$ *m/z*, calcd 547.2604, found 547.2600.

*4.8.3. Pyrimidone **34**.* Firstly, according to general procedure 4, the reaction was performed with pyrimidin-4-one **33** (114 mg, 0.22 mmol), 1 M TBAF solution in THF (0.66 ml, 3 equiv) and THF (3 ml) to afford the alcohol crude product. This intermediate was used directly in the next step. Then, this alcohol was oxidized by using general procedure 1 with IBX (92.4 mg, 1.5 equiv) and the 5/1 mixture THF/DMSO (6 ml) to afford **34** (47.3 mg, 53%, two steps) as a yellow viscous oil. ^1H NMR (300 MHz, $CDCl_3$) δ (ppm): 13.45 (br s, 1H), 8.31–8.25 (m, 2H), 7.59–7.47 (m, 3H), 7.37 (s, 1H), 6.84 (s, 1H), 3.98 (s, 3H), 3.85 (s, 3H), 3.71 (s, 3H), 3.28 (st, *J*=6.9 Hz, 1H), 1.24 (d, *J*=6.9 Hz, 6H). ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 193.1, 165.9, 162.8, 157.0, 156.0, 152.4, 145.5, 137.5, 132.4, 131.3, 129.0, 127.9, 125.8, 122.8, 111.3, 61.4, 61.1, 60.6, 27.1, 23.2. HRMS (ESI^+): $C_{23}H_{24}N_2O_5Na$ $[M+Na]^+$ *m/z*, calcd 431.1577, found 431.1579.

*4.8.4. Pyrimidone **35**.* According to general procedure 3, the reaction was performed with **34** (47.3 mg, 0.11 mmol), 1 M BBr_3 solution in DCM (1 ml, 9 equiv) and DCM (5 ml). A purification on silica gel (eluent: pentane/EA 7/3) afford **35** (6 mg, 14%) as orange solid. ^1H NMR (300 MHz, $CDCl_3$) δ (ppm): 12.92 (br s, 1H), 12.25 (s, 1H), 8.30 (d, *J*=7.1 Hz, 2H), 7.65–7.54 (m, 3H), 7.60 (s, 1H), 6.94 (s, 1H), 5.67 (br s, 1H), 4.08 (s, 3H), 3.23 (st, *J*=6.9 Hz, 1H), 1.15 (d, *J*=6.9 Hz, 6H). ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 194.9, 165.0, 161.2, 157.0, 151.3, 151.1, 136.8, 133.0, 132.8, 131.1, 129.2, 127.8, 121.3, 113.8, 113.6, 60.7, 26.9, 23.2. HRMS (ESI^+): $C_{21}H_{20}N_2O_5Na$ $[M+Na]^+$ *m/z*, calcd 403.1264, found 403.1264.

4.9. Preparation of phenolic pyridine-containing compound 38

*4.9.1. Pyridine **36**.* To a stirred solution of NH_4OAc (1.3 g, 20 equiv) and ethyl acetoacetate (214 μl, 2 equiv) in 15 ml EtOH at rt after 2 h and 30 min, was added **25** (475 mg, 0.85 mmol). The mixture was stirred at rt overnight. I_2 (43.2 mg, 0.2 equiv) was added and this mixture was stirred for another hour at 50 °C. It was then quenched with a saturated sodium thiosulfate solution. The mixture was extracted with EA, the organic phases dried over $MgSO_4$, and concentrated under reduced pressure. The crude product was purified on a silica gel column using the 9/1 mixture pentane/EA as eluent to afford the desired product **36** (398 mg, 70%) as a colorless viscous oil. ^1H NMR (300 MHz, $CDCl_3$) δ (ppm): 7.95 (s, 1H), 7.89 (d, *J*=8.6 Hz, 2H), 7.60 (d, *J*=8.6 Hz, 2H), 7.03 (s, 1H), 6.24 (s, 1H), 4.36–4.10 (m, 2H), 3.83 (s, 3H), 3.80 (s, 3H), 3.63 (s, 3H), 3.25 (st, *J*=6.9 Hz, 1H), 2.59 (s, 3H), 1.27 (t, *J*=7.2 Hz, 3H), 1.20 (d, *J*=6.9 Hz, 3H), 1.18 (d, *J*=6.9 Hz, 3H), 0.92 (s, 9H), 0.05 (s, 3H), −0.01 (s, 3H). ^{13}C

NMR (125 MHz, $CDCl_3$) δ (ppm): 168.0, 155.3, 155.0, 151.1, 149.1, 145.7, 136.7, 132.0, 130.6, 128.7, 125.7, 123.8, 120.7, 116.2, 69.2, 61.2, 61.1, 60.4, 60.2, 29.7, 26.8, 25.9, 25.8, 23.6, 23.5, 23.1, 18.3, 14.0, −4.8, −4.9. HRMS (ESI^+): $C_{34}H_{47}NO_6BrSiNa$ $[M+H]^+$ m/z, calcd 672.2356, found 672.2358.

4.9.2. Pyridine ***37****.* To a stirred solution of **36** (300 mg, 0.45 mmol) in CH_3CN (5 ml) at rt under nitrogen was added dropwise $BF_3{\cdot}OEt_2$ (114 μl, 2 equiv). The reaction mixture was heated to 50 °C and stirred for 1 h before quenching with water at rt and then extracted with EA. The organic layer was washed with saturated NaCl, dried over $MgSO_4$. After evaporation of the solvent, the residue was purified on a silica gel column using the 8/2 mixture pentane/EA as eluent to afford the desired product **37** (150 mg, 66%) as a colorless viscous oil. ^1H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.92 (d, J=8.6 Hz, 2H), 7.59 (d, J=8.6 Hz, 2H), 7.55 (s, 1H), 6.68 (s, 1H), 6.56 (s, 1H), 3.90 (s, 3H), 3.88 (s, 3H), 3.85 (s, 3H), 3.21 (m, J=6.9 Hz, 1H), 2.99 (s, 3H), 1.16 (d, J=6.9 Hz, 3H), 1.11 (d, J=6.9 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 169.5, 160.4, 159.6, 159.5, 152.7, 150.1, 146.3, 138.2, 137.1, 132.1, 129.2, 124.8, 123.3, 119.5, 118.4, 111.6, 78.3, 61.2, 61.0, 60.6, 27.1, 23.4, 23.3, 21.1. HRMS (ESI^+): $C_{26}H_{26}NO_5BrNa$ $[M+Na]^+$ m/z, calcd 534.0886, found 534.0887.

4.9.3. Pyridine ***38****.* According to general procedure 3, the reaction was performed with **37** (50 mg, 0.1 mmol), 1 M BBr_3 solution in DCM (1 ml, 10 equiv) and DCM (5 ml) to afford **38** (20 mg, 44%) as brown solid. ^1H NMR (300 MHz, acetone-d_6) δ (ppm): 8.13 (d, J=8.8 Hz, 2H), 7.86 (s, 1H), 7.67 (d, J=8.8 Hz, 2H), 7.62 (br s, 1H), 6.74 (s, 1H), 6.57 (s, 1H), 3.18 (m, J=6.9 Hz, 1H), 2.88 (s, 3H), 1.14 (d, J=6.9 Hz, 3H), 1.09 (d, J=6.9 Hz, 3H). ^{13}C NMR (100 MHz, acetone-d_6) δ (ppm): 171.0, 163.3, 160.4, 160.3, 146.9, 145.2, 139.3, 133.8, 131.2, 129.2, 125.9, 120.9, 118.3, 116.1, 113.6, 80.6, 28.7, 24.1, 24.0, 22.0. HRMS (ESI^+): $C_{23}H_{21}NO_5Br$ $[M+H]^+$ m/z, calcd 470.0603, found 470.0605.

4.10. BRET assay

Hela cells were seeded on 6-well plates and transfected with 200 ng/well of plasmid pRLuc-Bax coding for BRET donor and 1 μg/well of peYFP-Bcl-xL coding for BRET acceptor (or with pCMV-Bcl-xL for control). Twenty-four hours after transfection, cells were trypsinized and re-seeded into white 96 flat well plate, incubated for another day, and then treated with drugs for 16 h at 10 μM. Light emission at 485 nm and 530 nm was measured consecutively by using the Mithras fluorescence-luminescence detector LB 940 (Berthold) after adding the luciferase substrate, coelenterazine H (Uptima) at a final concentration of 5 μM. BRET ratios were calculated as described.[22]

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Supplementary data

Supplementary data associated with this article (characterization data: ^1H and ^{13}C NMR spectra) are available. Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.tet.2013.11.060.

References and notes

1. (a) Ellis, H. M.; Horvitz, H. R. *Cell* **1986**, *44*, 817; (b) Hengartner, M. O.; Horvitz, H. R. *Cell* **1994**, *76*, 665; (c) Vaux, D. L.; Weissman, I. L.; Kim, S. K. *Science* **1992**, *258*, 1955; (d) Meier, P.; Finch, A.; Evan, G. *Nature* **2000**, *407*, 796.
2. LeTai, A. G. *Nat. Rev. Cancer* **2008**, *8*, 121.
3. For reviews targeting protein−protein interaction of Bcl-2 family, see: (a) Juin, P.; Geneste, O.; Raimbaud, E.; Hickman, J. A. *Biochim. Biophys. Acta* **2004**, *1644*, 251; (b) Walensky, L. D. *Cell Death Differ.* **2006**, *13*, 1339; (c) Verdine, G. L.; Walensky, L. D. *Clin. Cancer Res.* **2007**, *13*, 7264; (d) Zhang, L.; Ming, L.; Yu, J. *Drug Resist. Updates* **2007**, *10*, 207; (e) Zeitlin, B. D.; Zeitlin, I. J.; Nör, J. E. *J. Clin. Oncol.* **2008**, *26*, 4180; (f) Lessene, G.; Czabotar, P. E.; Colman, P. M. *Nat. Rev. Drug Discov.* **2008**, *7*, 989; (g) Marzo, I.; Naval, J. *Biochem. Pharmacol.* **2008**, *76*, 939; (h) Azmi, A. S.; Mohammad, R. M. *J. Cell. Physiol.* **2009**, *218*, 13; (i) Chonghaile, T. N.; Letai, A. *Oncogene* **2009**, *27*, S149; (j) Vogler, M.; Dinsdale, D.; Dyer, M. J. S.; Cohen, G. M. *Cell Death Differ.* **2009**, *16*, 360; (k) Leber, B.; Geng, F.; Kale, J.; Andrews, D. W. *Exp. Rev. Mol. Med.* **2010**, *12*, e28; (l) Balakrishnan, K.; Gandhi, V. *Invest. New Drugs* **2013**, doi:10.107/s10637-013-0002-4, and references cited therein.
4. (a) Oltersdorf, T.; Elmore, S. W.; Shoemaker, A. R.; Armstrong, R. C.; Augeri, D. J.; Belli, B. A.; Bruncko, M.; Deckwerth, T. L.; Dinges, J.; Hajduk, P. J.; Joseph, M. K.; Kitada, S.; Korsmeyer, S. J.; Kunzer, A. R.; Letai, A.; Li, C.; Mitten, M. J.; Nettesheim, D. G.; ShiChung, Ng.; Nimmer, P. M.; O'Connor, J. M.; Oleksijew, A.; Petros, A. M.; Reed, J. C.; Shen, W.; Tahir, S. K.; Thompson, C. B.; Tomaselli, K. J.; Wang, B.; Wendt, M. D.; Zhang, H.; Fesik, S. W.; Rosenberg, S. H. *Nature* **2005**, *435*, 677; (b) Moore, V. D. G.; Brown, J. R.; Certo, M.; Love, T. M.; Novina, C. D.; Letai, A. *J. Clin. Invest.* **2007**, *117*, 112; (c) Deng, J.; Carlson, N.; Takeyama, K.; Cin, P. D.; Shipp, M.; Letai, A. *Cancer Cell* **2007**, *12*, 171; (d) Konopleva, M.; Contractor, R.; Tsao, T.; Samudio, I.; Ruvolo, P. P.; Kitada, S.; Deng, X.; Zhai, D.; Shi, Y.-X.; Sneed, T.; Verhaegen, M.; Soengas, M.; Ruvolo, V. R.; McQueen, T.; Schober, W. D.; Watt, J. C.; Jiffar, T.; Ling, X.; Marini, F. C.; Harris, D. D.; Dietrich, M.; Estrov, Z.; McCubrey, J.; May, W. S.; Reed, J. C.; Andreeff, M. *Cancer Cell* **2006**, *10*, 375.
5. (a) van Delft, M. F.; Wei, A. H.; Mason, K. D.; Vandenberg, C. J.; Chen, L.; Czabotar, P. E.; Willis, S. N.; Scott, C. L.; Day, C. L.; Cory, S.; Adams, J. M.; Roberts, A. W.; Huang, D. C. S. *Cancer Cell* **2006**, *10*, 389; (b) Thomas, L. W.; Lam, C.; Edwards, S. W. *FEBS Lett.* **2010**, *584*, 2981; (c) Warr, M. R.; Shore, G. C. *Curr. Mol. Med.* **2008**, *8*, 138.
6. Wei, G.; Margolin, A. A.; Haery, L.; Brown, E.; Cucolo, L.; Julian, B.; Shehata, S.; Kung, A. L.; Beroukhim, R.; Golub, T. R. *Cancer Cell* **2012**, *21*, 547.
7. Gautier, F.; Guillemin, Y.; Cartron, P. F.; Gallenne, T.; Cauquil, N.; Le Diguarher, T.; Casara, P.; Vallette, F. M.; Manon, S.; Hickman, J. A.; Geneste, O.; Juin, P. *Mol. Cell. Biol.* **2011**, *31*, 832.
8. Lessene, G.; Czabotar, P. E.; Sleebs, B. E.; Zobel, K.; Lowes, K. N.; Adams, J. M.; Baell, J. B.; Colman, P. M.; Deshayes, K.; Fairbrother, W. J.; Flygare, J. A.; Gibbons, P.; Kersten, W. J. A.; Kulasegaram, S.; Moss, R. M.; Parisot, J. P.; Smith, B. J.; Street, I. P.; Yang, H.; Huang, D. C. S.; Watson, K. G. *Nat. Chem. Biol.* **2013**, *9*, 390.
9. (a) Amblard, F.; Govindarajan, B.; Lefkove, B.; Rapp, K. L.; Detorio, M.; Arbiser, J. L.; Schinazi, R. F. *Bioorg. Med. Chem. Lett.* **2007**, *17*, 4428; (b) Kampa, M.; Nifli, A.-P.; Notas, G.; Castanas, E. *Rev. Physiol. Biochem. Pharmacol.* **2007**, *159*, 79; (c) Brough, P. A.; Aherne, W.; Barril, X.; Borgognoni, J.; Boxall, K.; Cansfield, J. E.; Cheung, K.-M. J.; Collins, I.; Davies, N. G. M.; Drysdale, M. J.; Dymock, B.; Eccles, S. A.; Finch, H.; Fink, A.; Hayes, A.; Howes, R.; Hubbard, R. E.; James, K.; Jordan, A. M.; Lockie, A.; Martins, V.; Massey, A.; Matthews, T. P.; McDonald, E.; Northfield, C. J.; Pearl, L. H.; Prodromou, C.; Ray, S.; Raynaud, F. I.; Roughley, S. D.; Sharp, S. Y.; Surgenor, A.; Walmsley, D. L.; Webb, P.; Wood, M.; Workman, P.; Wright, L. *J. Med. Chem.* **2008**, *51*, 196; (d) Bertini, S.; Calderone, V.; Carboni, I.; Maffei, R.; Martelli, A.; Martinelli, A.; Minutolo, F.; Rajabi, M.; Testai, L.; Tuccinardi, T.; Ghidoni, R.; Macchia, M. *Bioorg. Med. Chem.* **2010**, *18*, 6715; (e) Quideau, S.; Deffieux, D.; Douat-Casassus, C.; Pouységu, L. *Angew. Chem., Int. Ed.* **2011**, *50*, 586.
10. (a) James, D. F.; Prada, C. E.; Castro, J. E.; Kipps, T. J. *Blood* **2005**, *106*, 835A; (b) James, D. F.; Castro, J. E.; Loria, O.; Prada, C. E.; Aguillon, R. A.; Kipps, T. J. *Proc. Am. Soc. Clin. Oncol.* **2006**, *24*, 362S (abstr. 6605); (c) Zhao, Y.; Gounder, M.; Lin, H.; Harris Addo, K.; Taber Levinson, K.; LaRosiliere, M.; Goodin, S.; Moss, R. A.; Tan, A. R.; Stein, M. N. *J. Clin. Oncol.* **2011**, *29*, 7S (abstr. 169); (d) Stein, M. N.; Khan, I.; Hussain, M.; Liu, G.; Wilding, G.; Posadas, E. M.; Stadler, W. M.; Jeyamohan, C.; Eddy, S.; DiPaola, R. S. *J. Clin. Oncol.* **2011**, *29*, 7S (abstr. 137).
11. (a) Wang, S. PCT Int. Appl., 2006, WO2006023778A2. (b) Wang, G.; Coleska, Z. N.; Yang, C.-Y.; Wang, R.; Tang, G.; Guo, J.; Shangary, S.; Qiu, S.; Gao, W.; Yang, D.; Meagher, J.; Stuckey, J.; Krajewski, K.; Jiang, S.; Roller, P. P.; Abaan, H. O.; Tomita, Y.; Wang, S. *J. Med. Chem.* **2006**, *49*, 6139; (c) Tang, G.; Yang, C.-Y.; Coleska, Z. N.; Guo, J.; Qiu, S.; Wang, R.; Gao, W.; Wang, G.; Stuckey, J.; Krajewski, K.; Jiang, S.; Roller, P. P.; Wang, S. *J. Med. Chem.* **2007**, *50*, 1723; (d) Tang, G.; Coleska, Z. N.; Qiu, S.; Yang, C.-Y.; Guo, J.; Wang, S. *J. Med. Chem.* **2008**, *51*, 717.
12. Varadarajan, S.; Vogler, M.; Butterworth, M.; Walensky, L. D.; Cohen, G. M. *Cell Death Differ.* **2013**, , http://dx.doi.org/10.1038/cdd.2013.79
13. (a) Manero, F.; Gautier, F.; Gallenne, T.; Cauquil, N.; Grée, D.; Cartron, P.-F.; Geneste, O.; Grée, R.; Vallette, F. M.; Juin, P. *Cancer Res.* **2006**, *66*, 2757; (b) Oliver, L.; Mahé, B.; Grée, R.; Vallette, F. M.; Juin, P. *Leuk. Res.* **2007**, *31*, 859; (c) Grée, D.; Vorin, S.; Manthati, V. L.; Caijo, F.; Viault, G.; Manero, F.; Juin, P.; Grée, R. *Tetrahedron Lett.* **2008**, *49*, 3276; (d) Viault, G.; Grée, D.; Roisnel, T.; Chandrasekhar, S.; Grée, R. *Tetrahedron* **2009**, *65*, 10149.
14. Vo, D. D.; Gautier, F.; Juin, P.; Grée, R. *Eur. J. Med. Chem.* **2012**, *51*, 286.
15. Other approaches towards Bcl-xL inhibitors, like BH3 helix mimetics, are under study; see for instance: (a) Ernst, J. T.; Becerril, J.; Park, H. S.; Yin, H.; Hamilton, A. D. *Angew. Chem., Int. Ed.* **2003**, *42*, 535; (b) Yap, J. L.; Cao, X.; Vanommeslaeghe, K.; Jung, K. Y.; Peddaboina, C.; Wilder, P. T.; Nan, A.; MacKerell, A. D., Jr.; Smythe, W. R.; Fletcher, S. *Org. Biomol. Chem.* **2012**, *10*,

2928; (c) Cao, X.; Yap, J. L.; Newell-Rogers, M. K.; Peddaboina, C.; Jiang, W.; Papaconstantinou, H. T.; Jupitor, D.; Rai, A.; Jung, K. Y.; Tubin, R. P.; Yu, W.; Vanommeslaeghe, K.; Wilder, P. T.; Mackerell, A. D., Jr.; Fletcher, S.; Smythe, R. W. *Mol Cancer* **2013**, *12*, 42; (d) Kutzki, O.; Park, H. S.; Ernst, J. T.; Orner, B. P.; Yin, H.; Hamilton, A. D. *J. Am. Chem. Soc.* **2002**, *124*, 11838 and references cited therein.

16. (a) For a general review on click chemistry see: Kolb, H. C.; Finn, M. G.; Sharpless, K. B. *Angew. Chem., Int. Ed.* **2001**, *40*, 2004 and references cited therein; see also (b) Huisgen, R. *Angew. Chem., Int. Ed. Engl.* **1968**, *7*, 321; (c) Huisgen, R. In *1,3-Dipolar Cycloaddition Chemistry*; Padwa, A., Ed.; John Wiley & Sons: New York, NY, 1984; Vol. 1.
17. (a) Angelo, N. G.; Arora, P. S. *J. Am. Chem. Soc.* **2005**, *127*, 17134; (b) Angelo, N. G.; Arora, P. S. *J. Org. Chem.* **2007**, *72*, 7963; (c) Jochim, A. L.; Miller, S. E.; Angelo, N. G.; Arora, P. S. *Bioorg. Med. Chem. Lett.* **2009**, *19*, 6023; (d) Ko, E.; Liu, J.; Perez, L. M.; Lu, G.; Schaefer, A.; Burgess, K. *J. Am. Chem. Soc.* **2011**, *133*, 462 and references cited therein.
18. (a) Medwid, J. B.; Paul, R.; Baker, J. S.; Brochman, J. A.; Du, M. T.; Hallett, W. A.; Hanifin, J. W.; Hardy, R. A., Jr.; Tarrant, M. E.; Torley, L. W.; Wrenn, S. *J. Med. Chem.* **1990**, *33*, 1230 See also: (b) Dhuguru, J.; Gheewala, C.; Saleesh Kumar, N. S.; Wilson, J. N. *Org. Lett.* **2011**, *13*, 4188 and references cited therein.
19. Bohlmann, F.; Rahtz, D. *Chem. Ber.* **1957**, *90*, 2265.
20. (a) Bagley, M. C.; Glover, C.; Chevis, E. D. *Synlett* **2005**, 649; (b) Bagley, M. C.; Glover, C.; Merritt, E. A. *Synlett* **2007**, 2459 and references cited therein.
21. Vo, D. D.; Gautier, F.; Barillé-Nion, S.; Juin, P.; Grée, R.; Levoin, N., manuscript in preparation.
22. Terrillon, S.; Durroux, T.; Mouillac, B.; Breit, A.; Ayoub, M. A.; Taulan, M.; Jockers, R.; Barberis, C.; Bouvier, M. *Mol. Endocrinol.* **2003**, *17*, 677.