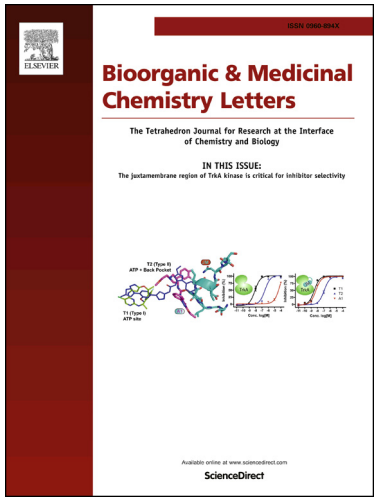


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PII: S0960-894X(17)30302-5
DOI: http://dx.doi.org/10.1016/j.bmcl.2017.03.054
Reference: BMCL 24806

To appear in: *Bioorganic & Medicinal Chemistry Letters*

Received Date: 20 January 2017
Revised Date: 20 March 2017
Accepted Date: 21 March 2017

Please cite this article as: Ronco, C., Millet, A., Plaisant, M., Abbe, P., Hamouda-Tekaya, N., Rocchi, S., Benhida, R., Structure activity relationship and optimization of *N*-(3-(2-aminothiazol-4-yl)aryl)benzenesulfonamides as anti-cancer compounds against sensitive and resistant cells, *Bioorganic & Medicinal Chemistry Letters* (2017), doi: http://dx.doi.org/10.1016/j.bmcl.2017.03.054

# Structure activity relationship and optimization of *N*-(3-(2-aminothiazol-4-yl)aryl)benzenesulfonamides as anti-cancer compounds against sensitive and resistant cells

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**Abstract:** We recently described a new family of bioactive molecules with interesting anti-cancer activities: the N-(4-(3-aminophenyl)thiazol-2-yl)acetamides. The lead compound of the series (**1**) displays significant anti-proliferative and cytotoxic activities against a panel of cancer cell lines, either sensitive or resistant to standard treatments. This molecule also shows a good pharmacological profile and high in vivo potency towards mice xenografts, without signs of toxicity on the animals. In the present article, we disclose the structure-activity relationships of this lead compound, which have provided clear information about the replacement of the acetamide function and the substitution pattern of the benzenesulfonamide ring. An improved high-yielding synthetic procedure towards these compounds has also been developed. Our drug design resulted in potency enhancement of **1**, our new optimized lead compound being **19**. These findings are of great interest to further improve this scaffold for the development of future clinical candidates.

**Keywords:** Thiazolyl-benzenesulfonamides, Structure activity relationship, Lead optimization, Drug resistance, Cancer, Autophagy and Apoptosis.

**Main Text:**

Despite constant research progress, cancer remains the leading cause of death in developed countries.[1] Classical radio- and chemotherapies based on DNA-damaging methods usually suffer from low success rates and limited benefit for patients because of severe adverse effects.[2,3] The advent of targeted therapies has improved the clinical outcomes of certain patients with various types of cancer.[4,5] However, rapid emergence of resistance against these agents and particularly toward kinase inhibitors is frequently observed contributing therefore to treatment failure.[6-9] In this context, the development of new bioactive molecules featuring a new mode of action is urgently needed to overcome drug resistance.[10,11]

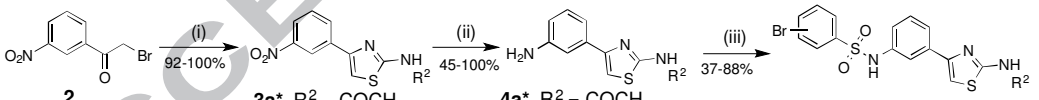
We recently described a new class of compounds, belonging to the N-(4-(3-aminophenyl)thiazol-2-yl)acetamides family, that showed significant cytotoxic activities on different cancers, including cells resistant to the standard treatments.[12-15] Our previous results pointed out the importance of a sulfonamide over an amide link to retain the biological activity, and suggested a preference for substituted

phenyl groups attached to the sulfonamide, over heteroaromatics. The most active compound of the series (**1,** Figure 1), which bears a 4-(oct-1-yn-1-yl) chain, displayed high potency towards a panel of sensitive and resistant cells, both in vitro and in vivo models.[12,13,16] However, the exact contribution of the alkyne-side chain and the acetamide group ($R^1$ and $R^2$, Figure 1) to the overall activity was not clearly established. To this end, we report herein the synthesis and the biological evaluation of a new set of analogues aimed at improving the bioactivity and at deciphering the structure-activity relationships of this class of compounds, on a melanoma A375 cell line model. Two types of analogues have been prepared depending on the modified moiety (Figure 1). The first one explores the modification of the octyn-1-yl chain on the phenyl ring, with a focus on the importance of the presence of the alkyne function, the substitution position, and the size of the hydrophobic chain. The second aimed at studying the effect of the acetamide group.


**Figure 1**. Structure of previous lead compound **1** and the envisioned modifications.

To this end, four new aryl bromide precursors **5a-c** and **6** were synthesized using a four-steps sequence: α-bromination / Hantzsch thiazole coupling / nitro reduction / sulfonylation (Scheme 1). These syntheses were performed from commercially available 3-nitroacetophenone following previously described or adapted procedures.[17-20] Briefly, after quantitative $AlCl_3$-catalyzed α-bromination of 3-nitroacetophenone, Hantzsch thiazole cyclocondensation with different suitable thioureas was performed with high yields to get the corresponding thiazoles **3a-c** (Scheme 3).[16-18] The nitro groups were subsequently reduced with $NaBH_4$-Pd/C to afford the corresponding anilines **4a-c**. Coupling with the suitable sulfonyl chlorides under standard conditions afforded bromosulfonamides **5a-c** and **6**.

**Scheme 1**. Synthesis of intermediates **3a-c, 4a-c, 5a-c** and **6.**

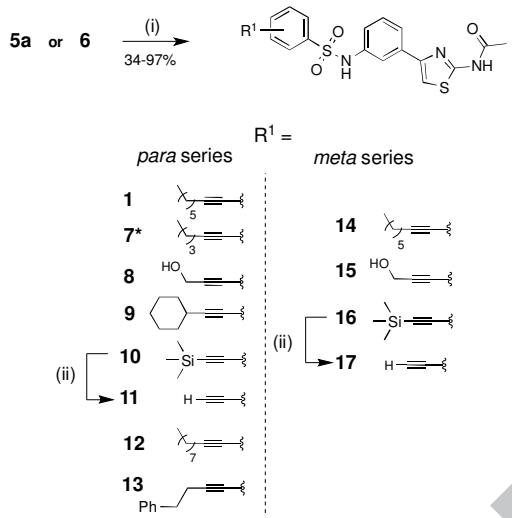



Reagents and conditions: (i) $Br_2$, $AlCl_3$, $Et_2O$, 0°C to r.t., 1 h; (ii) Corresponding thiourea, EtOH, 80°C, 2 h; (iii) $NaBH_4$, 10% Pd/C; MeOH, 0°C to r.t., 3 h; (iv) 3- or 4-bromobenzenesulfonyl chloride, $Et_3N$, DMF, r.t., 1 h. * Already described compound[12]

The first set of analogues was prepared to assess the impact of the variation of the oct-1-yn-1-yl chain on the biological activity. Thus, derivatives bearing various substituted alkynyl, alkenyl and alkyl chains of different sizes were synthetized (Scheme 2). The substitution pattern in *meta* or *para* position was also evaluated through the synthesis of both isomers for several compounds.

Notably, the synthetic route towards these compounds was revisited and optimized, particularly for the Sonogashira coupling reaction step. Whereas our previous coupling conditions using an aryl iodide and a Pd(II) source led to low and non-reliable yields, the replacement by a Pd(0) catalyst with aryl bromide was significantly more efficient. From precursors **5a** and **6**, optimal Sonogashira coupling conditions using $Pd(PPh_3)_4$ and CuI in a mixture of benzene and triethylamine allowed the preparation of derivatives **7-10** and **12-16** with significantly improved yields compared to our previous procedure using $Pd(OAc)_2$ and a iodo aryl compound (71-88% *vs* 25-35%). Subsequently the trimethylsilyl derivatives **10** and **16** were deprotected using $K_2CO_3$ in methanol to afford true alkynes **11** and **17** (Scheme 2).

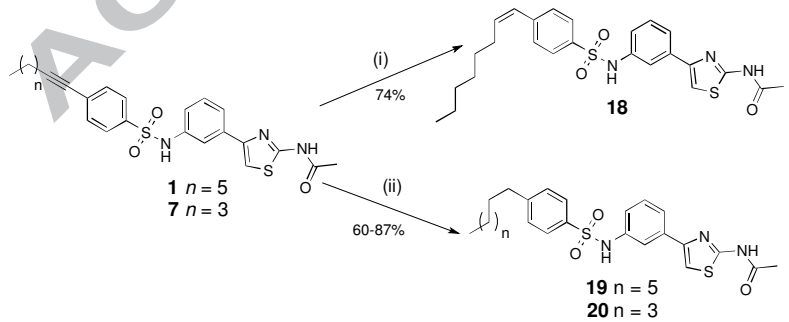
**Scheme 2**. Synthesis of derivatives **7-17**.




Reagents and conditions: (i) corresponding alkyne, $Pd(PPh_3)_4$, CuI, $Et_3N$/benzene, 1/1: v/v, 70°C, 2-4 h; (ii) $K_2CO_3$, MeOH/$CH_2Cl_2$, 1/1: v/v, 14 h.* Already described compound[12]

The alkene **18** and alkanes **19-20** were prepared by catalytic hydrogenation of the corresponding alkynes **1** or **7** (Scheme 3). **18** was synthesized by partial hydrogenation of **1** catalyzed by Lindlar palladium with satisfying 74% yield. Alkanes **19** and **20** were prepared by full reduction of the triple bond of respectively **1** and **7** in the presence of $H_2$/Pd/C.

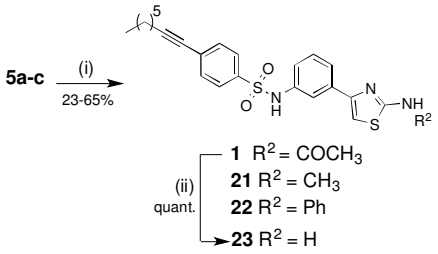
**Scheme 3**. Synthesis of derivatives **18-20**.




Reagent and conditions: (i) Pd Lindlar, $H_2$ (1 atm), MeOH, r.t., 2 h; (ii) 10% Pd/C, $H_2$ (1 atm), MeOH, r.t, 10 to 20 min.

The second set of analogues was prepared to study modifications on the aminothiazole function. Thus, *N*-phenyl, *N*-methyl and free aniline derivatives **21**, **22** and **23** were synthesized from bromosulfonamide precursors **5a-c** by using the above described optimized Sonogashira coupling reaction procedure (Scheme 4). Free aniline analogue **23** was obtained from **1**, after the acetyl group cleavage using aqueous HCl in ethanol at 80°C.

**Scheme 4**. Synthesis of derivatives **21-23**.




Reagents and conditions: (i) Oct-1-yne, $Pd(PPh_3)_4$, CuI, $Et_3N$/benzene, 1/1: v/v, 70°C, 2-4 h; (ii) 2M aq.HCl/EtOH, 1/1: v/v, 80°C, 1h30.

Therefore, nineteen analogues of **1** were synthesized and fully characterized. They were divided into two groups depending on the modified region. Derivatives of group **A** include compounds **5-20** and present modifications on the benzenesulfonamide moiety, whereas derivatives **21-23** belong to group **B** and are modified on the aminothiazole.

The presented analogues have been designed to explore several structural modifications of the lead compound **1**. The length of the oct-1-yn-1-yl chain was evaluated through derivatives **1** *vs* **6-7-12** and **19-20**, whereas its nature was evaluated with derivatives **8-11** and **13**. The necessity of the presence of the triple bond – as it is or though possible oxidative metabolism thereof – was estimated through analogues **1** *vs* **8, 11, 18, 19** and **20**. The orientation of the chain was evaluated with different *meta* and *para* isomers bearing the same chain: **1/14**, **5a/6**, **11/17**, and **8/15**. Finally, the aminothiazole substitution was probed with derivatives **1** *vs* **21**, **22** and **23**.

We first based our SAR study on viability assays on A375 melanoma cells. Indeed, melanoma, an aggressive form of skin cancer, was used as a cancer model as (i) its resistance to recent B-Raf inhibitors is a major concern, and (ii) because it still displays one of the highest mortality rates.[9] Derivatives of groups **A** and **B** were incubated with melanoma cells for 48h at three different doses: 10 µM, 5 µM, and 1 µM and cell counting was performed following the trypan blue exclusion assay method.

The cell viabilities of group **A** and **B** are summarized in Table 1. We found that the bromo derivative **5a** was significantly less active than its already described bulkier iodo analogue[12] (25.6% vs <1% at 10 µM). A similar activity was obtained for the *meta*-bromo isomer **6**. The 3-hydroxyprop-1-yn-1-yl derivatives **8** and **15** showed a significant decrease of the activity with an EC50 ~ 10 µM. The terminal alkynes **11** and **17** displayed viabilities values in the same range than the reference compound **1**, slightly lower. Of note, the trimethylsilylated precursors **10** and **16** were somewhat more active than the corresponding terminal alkynes **11** and **17**. The *meta*-branched oct-1-yn-1-yl analogue showed similar activities compared to the parent compound **1** (*para*-substituted).

**Table 1**. Evaluation of the activity of group **A** and group **B** derivatives.

| Compound | 2-thiazole substituent | position | % Cell viabilitiy[a] | | |
|---|---|---|---|---|---|
| | | | 10 µM | 5 µM | 1 µM |
| **1** | *NH-acetyl* | *para* | 5.8 ± 7.3 | 12.8 ± 2.0 | 40.7 ± 2.0 |
| **5a** | - | *para* | 25.6 ± 11.2 | 19.7 ± 5.3 | n.a.[c] |
| **6** | - | *meta* | 36.0 ± 8.0 | 67.4 ± 7.3 | n.a.[c] |
| **7** | - | *para* | < 1.0[b] | 9.3 ± 2.0 | 73.2 ± 12.6 |
| **8** | - | *para* | 48.8 ± 4.9 | 99.3 ± 17.2 | 81.3 ± 10.1 |
| **9** | - | *para* | 1.2 ± 2.0 | 1.2 ± 2.0 | 52.3 ± 24.6 |
| **10** | - | *para* | < 1.0[b] | 4.2 ± 0.6 | 94.3 ± 10.5 |
| **11** | - | *para* | 1.2 ± 2.0 | 38.3 ± 4.9 | 59.2 ± 4.9 |
| **12** | - | *para* | < 1.0[b] | 8.9 ± 3.8 | 39.6 ± 14.9 |
| **13** | - | *para* | < 1.0[b] | 4.2 ± 3.0 | 11.5 ± 3.5 |
| **14** | - | *meta* | < 1.0[b] | 1.2 ± 2.0 | 56.9 ± 2.0 |
| **15** | - | *meta* | 45.3 ± 4.9 | 66.2 ± 7.0 | 85.4 ± 7.4 |
| **16** | - | *meta* | 5.8 ± 2.0 | < 1.0[b] | 61.6 ± 10.6 |
| **17** | - | *meta* | 18.6 ± 5.3 | 29.0 ± 8.8 | 74.3 ± 14.5 |
| **18** | - | *para* | 2.3 ± 2.0 | 2.3 ± 4.0 | 48.8 ± 4.9 |
| **19** | - | *para* | < 1.0[b] | < 1.0[b] | 34.8 ± 9.9 |
| **20** | - | *para* | < 1.0[b] | < 1.0[b] | 49.9 ± 7.3 |
| **21** | *NH-methyl* | *para* | 1.2 ± 2.0 | 8.1 ± 8.0 | 36.6 ± 7.4 |
| **22** | *NH-phenyl* | *para* | 5.8 ± 4.0 | 59.2 ± 6.0 | 87.1 ± 9.9 |
| **23** | $NH_2$ | *para* | 3.5 ± 3.5 | < 1.0[b] | 97.6 ± 9.9 |

[a] Cell viability on A375 melanoma cells after a 48 h treatment of the indicated compounds at the defined concentration relative to a DMSO control ± SD from three independent experiments, as determined by trypan blue exclusion assay. [b] No viable cells. [c] Not active.

These first data with different *meta*- and *para*-substituted analogues pointed out three important results. First, a bulky apolar group seems to be clearly preferred over a smaller group or a polar function. Second, from 6-carbons, the elongation of the apolar chain did not bring much improvement of the activity. Third, *meta* and *para*-isomers showed similar behaviors, suggesting that high activity could be provided through attachment of a bulky apolar substituent probably by the concomitant modification of the global activity of the molecules. Therefore, all the other analogues were synthesized by introducing the substitution only at the *para* position. To examine the effect of the triple bond and the chain length, derivatives **9**, **18**, **19** and **20** were evaluated. Compound **9** featuring a cyclohexyl-ended alkyne displayed better activity than the parent compound **1**. Similar results were obtained for the partially reduced Z-alkene. The most active compounds are those containing the fully reduced side chain, compounds **19** and **20,** with no cell survival at 5 µM. These latter data suggest that the presence of a triple bond is not required since the activity is mainly provided by a bulky apolar group.

Group **B** derivatives were then evaluated to test the effect of the amino function on the thiazole ring. The phenylaniline in **22** appeared slightly detrimental to the activity whereas the methyl analogue **21** and the free aniline **23** proved slightly more active. This data is of particular interest, considering that the potential cleavage of the acetamide function by plasmatic or cellular hydrolases might still deliver a very active compound. These preliminary results suggest a variation tolerance at this position, which could be taken into account for further modifications towards chemical biology purposes (fluorescence and biotin-labeling).

From these data, ten compounds proved more active than the parent compound **1**. The five most promising ones (**9**, **14**, **18**, **19**, **20**) were then evaluated at several concentrations to evaluate their dose-response profile (see Supplementary Material).

These assays clearly confirmed a similar or slightly improved activity of derivatives **9**, **14**, **18**, **19** and **20** compared to the reference compound, particularly for derivative **19** with EC50 ~ 0.5 µM. Following these results, we evaluated three of the most promising

compounds **18**, **19** and **20** against resistant melanoma cell lines as well as against one hematologic cancer (Chronic Myelogenous Leukemia, CML) and one solid cancer (pancreatic cancer). The focus on these particular cancers was driven by the high occurrence of resistance phenomena in these diseases. Moreover, CML is a largely studied and well characterized tumor cell model; and pancreatic cancer possess no targeted therapy option, its treatment relying on the only use of the nucleoside analogue gemcitabine, which displays low response rates, high toxicity, severe adverse effects and rapid resistance, leading to overall low benefit/risk rates for patients.[21-24] The growth inhibition was tested by viability measurements on seven human cancer cell lines: A375, A375 RIV and A375 R5C3 (melanoma), K562 and K562R (CML) and BxPC3 and MiaPaCa-2 (pancreas). Of note, four of these seven cell lines are resistant to the currently applied therapies. A375 R5C3 and A375 RIV are resistant to the B-Raf inhibitor vemurafenib (after excessive prolonged exposure to the drug respectively in vitro and in vivo, respectively); K562R cell line is resistant to BCR-Abl inhibitor imatinib; and MiaPaCa-2 cell line is resistant to gemcitabine. All these cell lines are particularly aggressive and the development of new agents targeting them is urgently needed. Viability assays were then performed for selected compounds **18**, **19** and **20** (Table 2).

**Table 2**. Evaluation of the activity of **18**, **19** and **20** against selected sensitive and resistant cell lines.

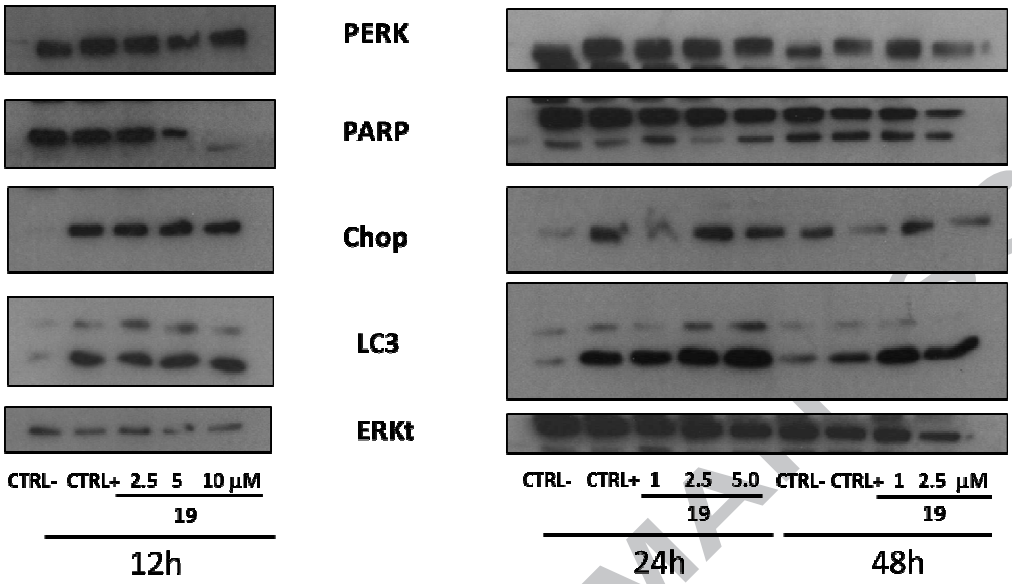
| Cell lines | Cancer | Status | *18* | *19* | *20* | Vemurafenib (5 µM)[12] | Imatinib (1 µM)[12] | Gemcitabine (0.1 µM)[12] |
|---|---|---|---|---|---|---|---|---|
| | | | % Cell viability (10 µM)[a] | | | | | |
| **A375** | *Melanoma* | *Sensitive* | < 1.0[b] | < 1.0[b] | 3.6 ± 0.7 | 44 ± 3.6 | - | - |
| **A375 RIV** | | *Resistant* | < 1.0[b] | 2.6 ± 0.3 | 3.4 ± 0.6 | 101.4 ± 1.9 | - | - |
| **A375 R5C3** | | *Resistant* | < 1.0[b] | 1.4 ± 0.7 | 1.4 ± 0.7 | 76.7 ± 3.3 | - | - |
| **K562** | *CML* | *Sensitive* | 8.9 ± 7.2 | 3.8 ± 0.3 | 23.2 ± 1.0 | - | 9.7 ± 0.5 | - |
| **K562R** | | *Resistant* | 41.1 ± 12.6 | 10.1 ± 4.9 | 41.6 ± 8.9 | - | 85.5 ± 17.7 | - |
| **BxPC3** | *Pancreatic* | *Sensitive* | 2.0 ± 0.3 | 4.9 ± 0.3 | 5.9 ± 1.0 | - | - | 2.0 ± 0.4 |
| **MiaPaCa-2** | | *Resistant* | 11.4 ± 1.2 | 11.4 ± 1.2 | 1.3 ± 0.3 | - | - | 86.5 ± 1.2 |

[a] Cell viability on the specified cells after a 48 h treatment of the indicated compounds at the defined concentration relative to a DMSO control ± SD from three independent experiments, as determined by trypan blue exclusion assay. [b] No viable cells.

Overall, the treatment with 10 µM of **18**, **19** and **20** strongly affected the cell viability of all tested cell lines. It appeared that the melanoma and the pancreatic cell lines were the most sensitive to the activity of these derivatives (Figure 2). Notably, these activities are much higher than those observed with vemurafenib, for which almost no response is observed in resistant cells A375 R5C3 and A375 RIV. For K562 CML cells, the compounds were generally less active than on melanoma A375 cells, but they still showed activities below 42% in all cases. Compound **19** was particularly interesting with a strong effect on both sensitive and resistant K562 cells compared to imatinib, which is completely inefficient. BxPC3 and MiaPaCa-2 pancreatic cancer cells were also strongly affected by the treatment with these compounds showing viabilities less than 11.4% for all three tested compounds. Especially interesting is their

high activity on resistant MiaPaCa-2 cells that are fully resistant to the gold-standard drug gemcitabine. Overall, **19** appeared to be the most potent compound and allowed a strong decrease in cell viability (<10%) in all tested cell lines. Strikingly, this compound retains a strong cytotoxic activity in all four resistant cell lines.

**Figure 2**. Western blot analysis of ER stress key markers by western blot analysis.




A375 melanoma cells were with compound **19** at 2.5, 5 and 10 µM. CTRL-: negative control (DMSO), CTRL+: positive control (HA15, 10 µM).[13] The cells were lysed at 12h, 24h and 48h and analyzed by western blotting using the indicated antibodies.

To confirm whether compound **19** displays the same ER stress related mechanism as already observed for compound **1**, we studied the key players of ER stress by western blot analysis on the lysate of A375 cells treated for different times with different concentrations of compound **19** (Figure 2). After 12 h of treatment with compound **19** at different concentrations, we observed a shift of PERK migration suggesting a phosphorylation of protein and a strongly increase in CHOP expression. This increase in expression and phosphorylation persisted after 48 h of treatment. These results suggest that compound **19** is able to induce an ER stress in A375 melanoma cells. We also observed that **19** induced a cleavage of PARP protein and conversion of LC3 I to LC3 II, attesting therefore for cancer cell death by a concomitant induction of apoptosis and autophagy induction.[25,26]

In summary, we reported the synthesis and biological evaluation of fifteen new N-(4-(3-aminophenyl)thiazol-2-yl)acetamides derivatives as anti-cancer compounds against sensitive and resistant cells. This study aimed at complementing and refining the structure-activity relationships of our previous lead compound **1**. Interestingly, both the chemical synthesis and the biological activity were significantly optimized. Our results showed that the activity of this class of compounds is mainly due to an increase in lipophilicity rather than to the alkyne geometry. Moreover, the tolerance towards acetamide variations is also useful information to explore this new chemical space in future analogues. Western blot analyses suggest that the activity relies on an ER stress related mechanism by a concomitant induction of apoptosis and autophagy cell deaths. Overall, these findings together with the potent activity of this class of

compounds notably on resistant cell lines are of great importance for the design and synthsesis of new potent bioactive molecules and anti-cancer agents,[27-31] in the search of a potential pre-clinical candidate.

**Acknowledgments**

This research was supported by CNRS, INSERM, University of Nice Sophia-Antipolis (AM grant), INSERM Transfert (COPOC grant), Canceropole PACA (Emerging projects) and ARC (contract n° SFI 20121205378). M. Plaisant is a recipient of "contrat INSERM Transfert". INSERM U1065, team 1 is «équipe labelisée ligue 2010 ».

Author Contributions: # Co-first authors, equal contribution. * Co-corresponding and co-last authors

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**Supplementary material**

Procedures, biological and spectral data of all compounds are provided in Supplementary material.