Bioorganic & Medicinal Chemistry Letters 21 (2011) 2149–2154

Contents lists available at ScienceDirect

Bioorganic & Medicinal Chemistry Letters

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

Synthesis of 5-arylated *N*-arylthiazole-2-amines as potential skeletal muscle cell differentiation promoters

Michael Schnürch [a,*], Birgit Waldner [a], Karlheinz Hilber [b], Marko D. Mihovilovic [a,*]

[a] Institute of Applied Synthetic Chemistry, Vienna University of Technology, Getreidemarkt 9/163-OC, A-1060, Vienna, Austria
[b] Center of Physiology and Pharmacology, Institute of Pharmacology, Medical University of Vienna, Währingerstraße 13, A-1090 Vienna, Austria

ARTICLE INFO

Article history:
Received 10 December 2010
Revised 24 January 2011
Accepted 27 January 2011
Available online 2 February 2011

Keywords:
Heterocycles
CH-activation
Cell differentiation
Bioactive compound

ABSTRACT

A series of *N*-arylthiazole-2-amines was prepared and their biological activity for the promotion of skeletal muscle cell differentiation was investigated, a process of significant importance in muscle regeneration. A versatile new synthetic route towards the target compounds was developed and the substrate scope of this methodology was investigated. Introduction of the 2-aminoaryl substituent was carried out via nucleophilic substitution reactions in excellent yields. Furthermore, the aryl in 5-position was introduced applying a direct arylation reaction, a major improvement compared to reported synthetic routes regarding atom efficiency and sustainability.

Molecules containing a thiazoleamine-moiety show a number of interesting biological activities depending on the different substituents and the substitution pattern at the thiazole ring.[1] Compounds of type **I** (Fig. 1) have been reported as potent histone deacetylase- and tyrosine kinase-inhibitors[1b] and *N*-phenylthiazoleamine derivatives are known as selective aurora kinase inhibitors.[1c] In addition, the ability to induce autophagic cell death in renal cancer cells has been reported in a recent publication for molecules of the general type **II**.[1d] A series of compounds (Fig. 1, **III**) has been introduced previously as orally active glutamate receptor antagonists (mGluRs), which are interesting targets for regulating glutamate transmission, aiming at the treatment of neurological and psychiatric diseases.[1e] Another interesting compound is Neuropathiazole (**IV**), a thiazole-4-amine, which was reported to induce neural differentiation of adult hippocampal neural progenitor cells.[2] Approaches to influence cell differentiation processes are of great potential and essentially two strategies have been described:[3] (i), de-differentiation of certain cell types back to multipotent progenitor cells which can then be differentiated again to other cell types; (ii) trans-differentiation of a cell to another cell type. The particular methods to influence differentiation processes are highly diverse. For example, lineage conversions can be induced through the introduction of certain transcription factors.[4] Additionally, it was demonstrated that the transfer of nuclei from either embryonic or somatic cell types can lead to the formation of all three germ layers and—most remarkably—even to the generation of entire new animals.[5] A recent development receiving much attention was the reprogramming of somatic cells to induced pluripotent stem cells (iPSCs) by the overexpression of a transcription factor cocktail.[6] These extremely remarkable results have certain disadvantages in view of future therapeutic application: a retrovirus is required to insert genes into the genome to ultimately stimulate de-differentiation into progenitor cells. As a consequence there is an unacceptable risk of permanent transgene integration into the genome. Additionally, two of the applied reprogramming factors (Klf4 and c-Myc) were reported as oncogenic in the original publication. However, this issue was already addressed by several

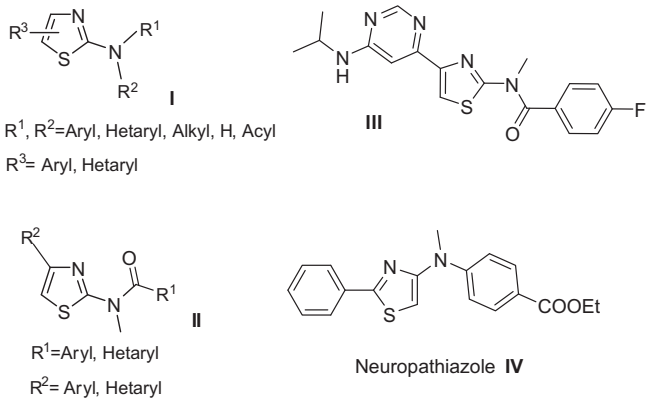


Figure 1.

* Corresponding author.
E-mail address: mmihovil@pop.tuwien.ac.at (M.D. Mihovilovic).

0960-894X/$ - see front matter © 2011 Elsevier Ltd. All rights reserved.
doi:10.1016/j.bmcl.2011.01.123

research groups and methods which avoid use of these two genes have been published.[6f,7] Still, both facts make the approval of such a method for medicinal applications problematic and eventually unlikely. Besides the aforementioned problems, iPSC reprogramming is still a slow and inefficient process.

An interesting alternative to influence cell differentiation is the application of synthetic small molecules. Some synthetic small molecules have been reported to induce cardiomyogenesis,[8] neurogenesis,[2,9] as well as de-differentiation,[10] and a series of publications has been dedicated to this topic in recent years.[11] The use of synthetic small molecules in therapies involving cell differentiation processes would be highly desirable since most approved drugs originate from the class of small chemical entities, and methods to test for activity and toxicology are well established. This suggests that processes leading to approval of these compounds for treatment in patients will be more facile compared to other methods such as inserting genes into the cells via a retrovirus.

Until now synthetic small molecules played only a minor role in accelerating cell differentiation processes. For example, adhesamine was reported to facilitate differentiation of primary cultured hippocampal neurons[12] and derivatives of wrenchnolol have been shown to activate gene expression in cells when tethered to a DNA binding molecule.[13] As outlined in Figure 2, these compounds represent quite complex molecules and substituting them with simpler scaffolds would be of great value.

Within this contribution, aryl-thiazole-amines are introduced as a class of compounds which displays the ability to significantly promote the differentiation process of C2C12 skeletal muscle cells. Conventional synthetic routes to access these products are often cumbersome and do not allow the efficient synthesis of compound-libraries that can be screened for biological activity. For example, cyclization reactions towards thiazoles such as the long established Hantzsch synthesis[14] usually give high yields, but require the preparation of suitable reaction partners for cyclization for every single compound. Therefore, a modular synthetic route which allows for the synthesis of a large number of derivatives from only a small set of building blocks is highly attractive. Within this contribution such a modular synthesis is reported and the scope of the method is demonstrated together with initial results from biological screening as differentiation accelerators.

2-Arylamino-5-aryl-thiazoles were considered as target compounds, since this compound class showed the potential to influence cell differentiation in a preliminary biological screening.

The conventional synthetic route to polysubstituted *N*-phenyl-2-thiazoleamines is outlined in Scheme 1.[1c–f,15] The first step consists of a cyclization reaction of *N*-phenylthiourea derivatives (**V**) and α-halocarbonyl compounds to form *N*-phenylthiazoleamine (**VI**). As the introduction of a halogen is required to perform cross-coupling reactions, a protecting group has to be installed prior to the bromination reaction avoiding formation of complex product mixtures.[16] However, bromination in 5-position of compounds of type **VII** usually proceeds efficiently.[16,17] Subsequently, several types of cross-coupling reactions (Suzuki–Miyaura, Stille, Negishi) can be performed to introduce different substituents on the thiazole ring; removal of the protecting group ultimately leads to target compounds **X**. This route has several disadvantages: Introduction of a substituent on the phenyl ring requires the synthesis of the corresponding thiourea derivative, which can be quite tedious or even impossible for some substituents. Additionally, the introduction of bromine for subsequent cross-coupling reactions is not desirable from the viewpoint of atom efficiency.

Therefore, an alternative route was envisioned to synthesize target compounds of general structure **X**. As first step, amination in position 2 of a 2-halothiazole was envisioned, followed by direct

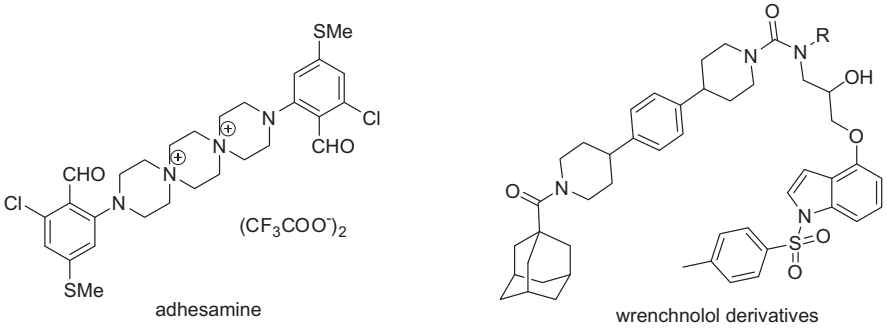
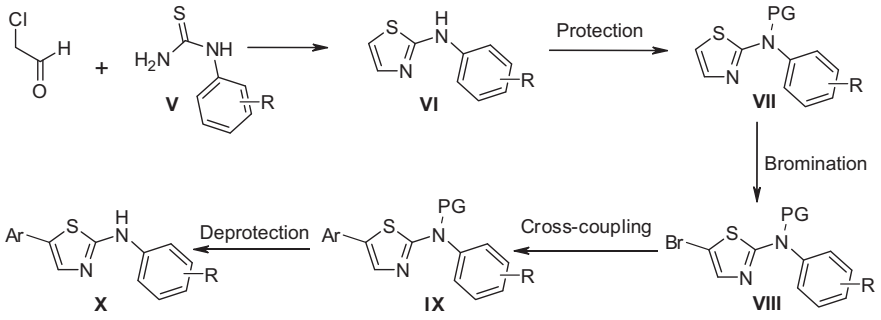


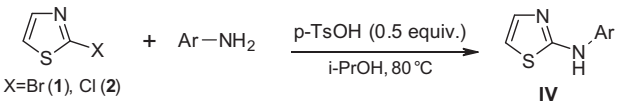
Figure 2.



Scheme 1.

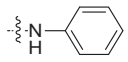
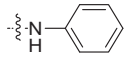
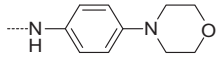
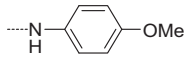
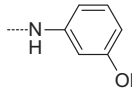
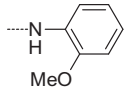
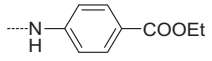
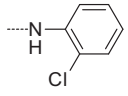
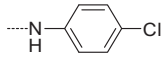
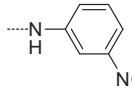
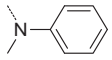
arylation in 5-position. Starting from either 2-chloro- or commercially available 2-bromothiazole, nitrogen incorporation in 2-position can be carried out via palladium catalyzed Buchwald–Hartwig amination reaction, a common method for the preparation of aryl- and hetarlyamines,[18] or by classical nucleophilic substitution. Since considerable efforts to optimize the Buchwald–Hartwig reaction did not provide good yields of the desired compounds due to by-product formation, nucleophilic substitution was favored (Scheme 2).[19]

Reactions were performed using 0.5 equiv of *p*-TsOH as catalyst in *i*-PrOH at 80 °C. A series of substituted anilines (2.0 equiv) was used as nucleophile utilizing 2-bromothiazole **1** or 2-chlorothiazole **2** as halide component. The protocol enabled access to substituted thiazoleamines in good to excellent yields for electron-poor as well as electron-rich aniline-derivatives (Table 1). Typically, yields >90% were obtained and only in two cases the isolated yield was <80% (entries 5 and 9). Regarding the halide leaving group, the initial reaction with simple aniline displayed only a negligible difference in yield comparing Cl and Br; both experiments required the same reaction time until completion (entries 1 and 2). Increasing the temperature to shorten the reaction time was avoided since then by-products were formed (although only in low amounts). Electron-rich aniline-derivatives (entries 3–6) reacted significantly slower, but only in the case of *m*-anisidine significant formation of secondary products was observed reducing the yield of **7** (48%; entry 5). The method tolerates a wide range of different functional groups (esters, nitro, chloro, methoxy, morpholino) and also sterically demanding *ortho*-substituted anilines were well tolerated with no loss in yield (entries 6 and 8). Also *N*-methylaniline gave an excellent yield as an example for a secondary amine.



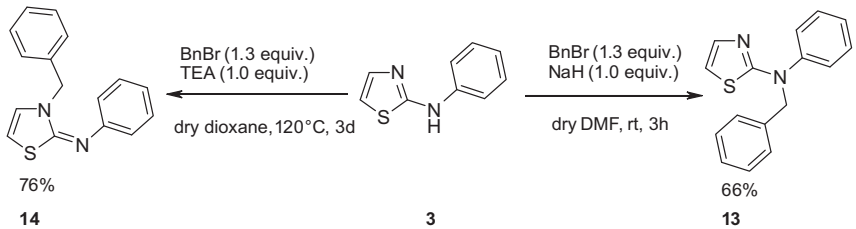
Scheme 2.

Table 1
Nucleophilic substitution towards 2-amino-thiazoles

Entry	X	Time	Ar	Product	Yield (%)
1	Br	3 d		**3**	90
2	Cl	3 d		**3**	84
3	Cl	3 w		**4**	87
4	Cl	3 w		**5**	97
5	Cl	3 w		**6**	48
6	Cl	3 w		**7**	85
7	Cl	1.5 d		**8**	97
8	Cl	2 d		**9**	95
9	Cl	2 d		**10**	76
10	Cl	1.5 d		**11**	98
11	Br	1.5 d		**12**	94

Direct arylation in 5-position of thiazoles has been reported previously[20] and gave superior results compared to Suzuki cross-coupling reactions in some cases.[21] This method is especially attractive since it avoids introduction of a leaving group for subsequent cross-coupling and increases the atom- and time- efficiency of a given synthetic route by concomitantly avoiding one reaction step. Several protocols have been reported for the direct arylation reaction of heterocyclic systems utilizing a conventional Pd(0) species/ligand combination as catalyst,[20b,22] in some cases with very low catalyst loadings (0.001 mol %) in the absence of a ligand using *N*,*N*-dimethylacetamide (DMAc) at 130 °C or 150 °C.[23]

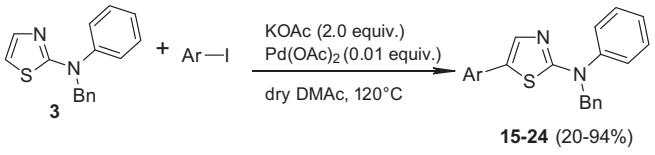
In order to avoid competitive arylation of the amino-functionality in 2-position a protective group had to be installed as direct arylation conditions are quite similar (Pd catalyst, base, aryl donor) to Buchwald–Hartwig amination conditions. This does not represent a disadvantage compared to a conventional cross coupling reaction route since for the introduction of, for example, bromine as leaving group a protective group has to be introduced as well. For our purpose, the benzyl-group was chosen due to its simple introduction and usually equally simple removal.[24] In this case the introduction of the benzyl-protecting group led to somewhat unexpected results: depending on the reaction conditions different products were formed starting from precursor **3** (Scheme 3). Using benzylbromide and 1.0 equiv of NaH as base in DMF at room temperature, the reaction was complete within 2–4 h and *N*-benzyl-*N*-phenylthiazoleamine **13**[25] was formed in the reaction as expected. However, when the protection was carried out with triethylamine as base in dioxane at 120 °C, the reaction took three days to complete and the resulting compound was isomeric *N*-(3-benzylthiazole-2(3*H*)-ylidene)aniline **14**[26] originating from benzylation of the endocyclic nitrogen atom. Similar behavior was recently reported in particular for aromatic electrophiles[27] and is significantly affected by substituents on the exocyclic nitrogen. In particular, strong electron-withdrawing substituents on the exocyclic heteroatom shift the equilibrium towards the imino-product. In addition, solvents with high dipole-moment favor formation of the more polarized imine product.[27c]



Scheme 3.

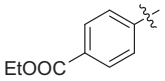
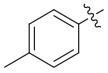
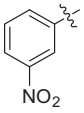
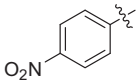
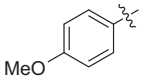
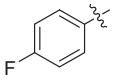
The present case is a unique situation for the benzyl protecting group. Using the weak base triethylamine deprotonation is a slow process and at high temperatures the equilibrium is shifted to the imino-product. When sodium hydride is used as a base, deprotonation occurs practically instantaneously and now the nucleophilicity of the deprotonated exocyclic nitrogen is much higher upon attack at benzyl bromide.

With precursor **13** in hand, direct arylation conditions were tested (Scheme 4; Table 2). When using iodobenzene as the halide component, best results were obtained using 1.0 equiv of **13**, 2.0 equiv of iodobenzene, 2.0 equiv KOAc as base and 1 mol % of $Pd(OAc)_2$ as catalyst in DMAc at 120 °C leading to an isolated yield of 85% of **15** (entry 1).[28] As similar transformation with bromobenzene displayed only low conversion to **15**, iodoaryls and iodoheteroaryls were used as aryl donors in the following reactions. Good yields were obtained using electron deficient aryliodides (entries 2, 3 and 9). However, nitro-substituents were generally not tolerated well resulting in decreased yields (entries 6 and 7). Also, 4-iodoanisole gave a lower yield even upon increasing catalyst loading to 10 mol % (entry 8); this goes in line with results obtained by Roger et al. when using *p*-bromoanisole in direct arylation reactions.[23b] Electronically neutral aryliodides also gave good yields (entries 1 and 5). Heterocyclic systems gave good results (entries 1 and 10) with the exception of 5-iodopyrazole (entry 11); this can be attributed to the presence of a free NH group and is in line with previous reports by Roger et al. on similar reactants containing free –NH groups.[23a] On the other hand, *ortho* substituents were well tolerated in direct arylation reactions (entries 2 and 4).



Scheme 4.

Table 2
Direct arylation of thiazoles 13 and 14

Entry	Time (h)	Ar	Product	Yield (%)
1	48		**15**	85
2	4		**16**	94
3	24		**17**	60
4	20		**18**	80
5	20		**19**	77
6	3		**20**	41
7	18		**21**	20
8	18		**22**	47[a]
9	20		**23**	78
10	20		**24**	85
11	48		**25**	0[b]

[a] 10 mol% of catalyst had to be applied.
[b] No conversion.

Figure 3.

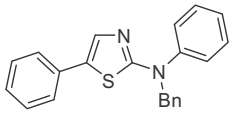
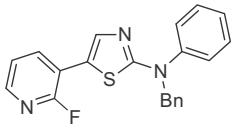
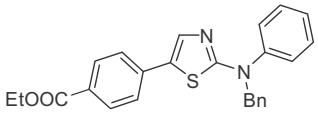
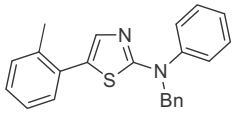
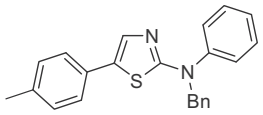
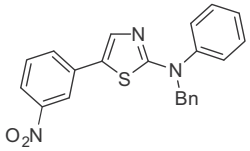
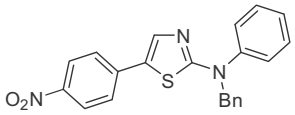
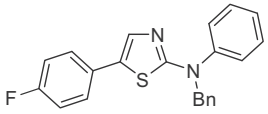
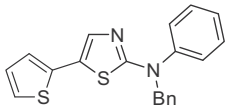
Target compounds were then tested regarding their biological activities in context of influencing the differentiation of C2C12 skeletal muscle cells. This cell line represents a well established model to study myogenic differentiation, which impacts muscle regeneration.[29] Within this preliminary study, only changes in cell morphology were monitored under the microscope at different time points (3, 5 and 7 days) after induction of differentiation by serum reduction,[30] whereby control cells were compared with single compound-treated cells. All C2C12 cells were incubated for two days in growth medium to reach a cell confluence of about 70%. Thereafter, differentiation medium without any compound was applied to one part of the cells (control group). The other cells were incubated in differentiation medium containing the compounds to be tested in a concentration of 5 μM (experimental groups). Prior to application, each single compound was dissolved in DMSO to obtain 20 mM stock solutions. Appropriate volumes of these stock solutions were then added to the differentiation medium to reach the desired final compound concentration of 5 μM. The differentiation medium applied to control cells contained equal amounts of DMSO. Each experiment was carried out as doublet, and four control experiments were performed.

After beginning of treatment with the compounds, cell cultures were incubated for 7 days at 37 °C. The medium was changed twice (after 3 days and 5 days of incubation). Morphological changes of cell cultures were documented by taking pictures after 3, 5, and 7 days (Fig. 3). Normally, 2–3 days after the induction of differentiation, undifferentiated C2C12 myoblasts begin to fuse to each other and form small multinuclear myotubes.[30] Larger longitudinal myotubes containing tens of nuclei usually appear after 5–6 days. Already after 3 days of treatment it could be observed that several of the tested compounds considerably promoted the differentiation process of muscle cells in comparison with the controls. Especially compound **24** proved to be highly active (Fig. 3). It can be observed that in cultures treated with **24** the number of large and well developed myotubes is considerably higher than in the control culture. In comparison to the pictures taken from the shown control experiment, the cells treated with **24** showed visible myotubes already after 3 days and a further enhancement of differentiation after 5 and 7 days. Morphological changes generated by all the tested compounds are summarized in Table 3. Except for compounds **18**, **19** and **21**, all the other compounds seemed to promote C2C12 cell differentiation whereby compound **24** was most effective.

In summary, an alternative, more practical pathway is presented for the synthesis of *N*,5-substituted thiazoleamine derivatives. The nucleophilic substitution reaction represents a high yielding and more practical alternative to the cyclization reaction to form *N*-phenylthiazoleamine **3** and derivatives thereof. After protection of the exocyclic nitrogen introduction of an aryl or heteroaryl substituent in 5-position was achieved by direct arylation. The particular reaction protocol utilized a ligand free system with $Pd(OAc)_2$ as catalyst and gave good to excellent yields in most cases with low catalyst loading. This route presents a three-step synthesis for 5-arylated-*N*-protected-*N*-phenylthiazoleamine derivatives, which is a significant improvement to already established strategies requiring 5+ steps.

With respect to biological activity of target compounds, a significant promotion of cell differentiation in C2C12 skeletal muscle cells was observed. Since enhanced myogenic differentiation in vitro goes along with improved muscle regeneration in vivo[29b,31] the active compounds identified in the present study could be useful to promote healing of muscles damaged by injury or disease. Further investigations regarding structure activity relationships aiming at the improvement of these results is currently underway in our laboratory.

Table 3
Morphological effect of test compounds on cell differentiation towards myotubes

Entry	Compound		Differentiation induction
1		**15**	Low
2		**16**	Moderate
3		**17**	Moderate
4		**18**	None
5		**19**	None
6		**20**	Moderate
7		**21**	None
8		**23**	Moderate
9		**24**	High

Acknowledgment

The authors thank Vienna University of Technology for supporting this project by an internal Micro Fund.

References and notes

1. (a) Biagetti, M.; Leslie, C. P.; Mazzali, A.; Seri, C.; Pizzi, D. A.; Bentley, J.; Genski, T.; Di Fabio, R.; Zonzini, L.; Caberlotto, L. *Bioorg. Med. Chem. Lett.* **2010**, *20*, 4741; (b) Mahboobi, S.; Dove, S.; Sellmer, A.; Winkler, M.; Eichhorn, E.; Pongratz, H.; Ciossek, T.; Baer, T.; Maier, T.; Beckers, T. *J. Med. Chem.* **2009**, *52*, 2265; (c) Andersen, C. B.; Wan, Y.; Chang, J. W.; Riggs, B.; Lee, C.; Liu, Y.; Sessa, F.; Villa, F.; Kwiatkowski, N.; Suzuki, M.; Nallan, L.; Heald, R.; Musacchio, A.; Gray, N. S. *ACS Chem. Biol.* **2008**, *3*, 180; (d) Hay, M. P.; Turcotte, S.; Flanagan, J. U.; Bonnet, M.; Chan, D. A.; Sutphin, P. D.; Nguyen, P.; Giaccia, A. J.; Denny, W. A. *J. Med. Chem.* **2010**, *53*, 787; (e) Satoh, A.; Nagatomi, Y.; Hirata, Y.; Ito, S.; Suzuki, G.; Kimura, T.; Maehara, S.; Hikichi, H.; Satow, A.; Hata, M.; Ohta, H.; Kawamoto, H. *Bioorg. Med. Chem. Lett.* **2009**, *19*, 5464; (f) Susnik, M. P.; Schnürch, M.; Mihovilovic, M. D.; Mereiter, K.; Stanetty, P. *Monatsh. Chem.* **2009**, *140*, 423.
2. Warashina, M.; Min, K. H.; Kuwabara, T.; Huynh, A.; Gage, F. H.; Schultz, P. G.; Ding, S. *Angew. Chem., Int. Ed.* **2006**, *45*, 591.
3. Graf, T.; Enver, T. *Nature* **2009**, *462*, 587.

4. Davis, R. L.; Weintraub, H.; Lasser, A. B. *Cell* **1987**, *51*, 987; Kulessa, H.; Frampton, J.; Graf, T. *Genes Dev.* **1995**, *9*, 1250.
5. (a) Gurdon, J. B.; Byrne, J. A. *Proc. Natl Acad. Sci. U.S.A.* **2003**, *100*, 8048; (b) Wilmut, I.; Schnieke, A. E.; McWhir, J.; Kind, A. J.; Campbell, K. H. *Nature* **1997**, *385*, 810; (c) Gurdon, J. B.; Melton, D. A. *Science* **2008**, *322*, 1811; (d) Hochedlinger, K.; Jaenisch, R. *Nature* **2002**, *415*, 1035.
6. (a) Takahashi, K.; Yamanaka, S. *Cell* **2006**, *126*, 663; (b) Maherali, N.; Hochedlinger, K. *Cell Stem Cell* **2008**, *3*, 595; (c) Lowry, W. E.; Richter, L.; Yachechko, R.; Pyle, A. D.; Tchieu, J.; Sridharan, R.; Clark, A. T.; Plath, K. *Proc. Natl. Acad. Sci. U.S.A.* **2008**, *105*, 2883; (d) Park, I. H.; Zhao, R.; West, J. A.; Yabuuchi, A.; Huo, H.; Ince, T. A.; Lerou, P. H.; Lensch, M. W.; Daley, G. Q. *Nature* **2008**, *451*, 141; (e) Takahashi, K.; Tanabe, K.; Ohnuki, M.; Narita, M.; Ichisaka, T.; Tomoda, K.; Yamanaka, S. *Cell* **2007**, *131*, 861; (f) Yu, J.; Vodyanik, M. A.; Smuga-Otto, K.; Antosiewicz-Bourget, J.; Frane, J. L.; Tian, S.; Nie, J.; Jonsdottir, G. A.; Ruotti, V.; Stewart, R.; Slukvin, I. I.; Thomson, J. A. *Science* **2007**, *318*, 1917.
7. Feng, B.; Jiang, J.; Kraus, P.; Ng, J. H.; Heng, J. C.; Chan, Y. S.; Yaw, L. P.; Zhang, W.; Loh, Y. H.; Han, J.; Vega, V. B.; Cacheux-Rataboul, V.; Lim, B.; Lufkin, T.; Ng, H.-H. *Nat. Cell Biol.* **2009**, *11*, 197.
8. (a) Wu, X.; Ding, S.; Ding, Q.; Gray, N. S.; Schultz, P. G. *J. Am. Chem. Soc.* **2004**, *126*, 1590; (b) Wu, X.; Ding, S.; Schultz, P. G. *PCT Int. Appl.* **2005**, WO 2005068437; CAN 143:172888.; (c) Willems, E.; Bushway, P. J.; Mercola, M. *Pediatr. Cardiol.* **2009**, *30*, 635.
9. (a) Barnard, J. H.; Collings, J. C.; Whiting, A.; Przyborski, S. A.; Marder, T. B. Chem. Eur. J. *2009* **2009**, *15*, 11430; (b) Williams, D. R.; Lee, M. R.; Song, Y. A.; Ko, S. K.; Kim, G. H.; Shin, I. *J. Am. Chem. Soc.* **2007**, *129*, 9258.
10. (a) Chen, S.; Zhang, Q.; Wu, X.; Schultz, P. G.; Ding, S. *J. Am. Chem. Soc.* **2004**, *126*, 410; (b) Chen, S.; Ding, S.; Schultz, P. G. PCT Int. Appl. 2005, WO, 2005047524 A2 20050526.
11. Feng, B.; Ng, J. H.; Heng, J. C.; Ng, H. H. *Cell Stem Cell* **2009**, *4*, 301; Chen, J. K.; Firestone, A. J.; Morgan, T. C.; Lee, M.-H.; Kimble *J. Nat. Chem. Biol.* **2010**, *6*, 102; Kim, N. R.; kang, S. K.; Ahn, H. H.; Kwon, S. W.; Park, W. S.; Kim, K. S.; Kim, S. S.; Jung, H. J.; Choi, S. U.; Ahn, J. H.; Kim, K. R. *J. Med. Chem.* **2009**, *52*, 7931; De Medina, P.; Paillasse, M. R.; Payre, B.; Silvente-Poirot, S.; Poirot, M. *J. Med. Chem.* **2009**, *52*, 7765; Firestone, A. J.; Chen, J. K. *ACS Chem. Biol.* **2010**, *5*, 15.
12. Hoshino, M.; Tsujimoto, T.; Yamazoe, S.; Uesugi, M.; Terada, S. *Biochem. J.* **2010**, *427*, 297.
13. Jung, D.; Shimogawa, H.; Kwon, Y.; Mao, Q.; Sato, S.-i.; Kamisuki, S.; Kigoshi, H.; Uesugi, M. *J. Am. Chem. Soc.* **2009**, *131*, 4774.
14. (a) Hantzsch, A. *Ber. Dtsch. Chem. Ges.* **1888**, *21*, 942; (b) Prakash, R.; Kumar, A.; Aggarwal, R.; Prakash, O.; Singh, S. P. *Synth. Commun.* **2007**, *37*, 2501; (c) Egan, R. S.; Tadanier, J.; Garmaise, D. L.; Gaunce, A. P. *J. Org. Chem.* **1968**, *33*, 4422; (d) Babadjamian, A.; Metzger, J.; Chanon, M. J. *J. Heterocycl. Chem.* **1975**, *12*, 643.
15. Zhao, M.; Yin, J.; Huffman, M. A.; McNamara, J. M. *Tetrahedron* **2006**, *62*, 1110.
16. Schnürch, M.; Khan, A. F.; Mihovilovic, M. D.; Stanetty, P. *Eur. J. Org. Chem.* **2009**, 3228.
17. (a) Khan, A. F.; Schnürch, M.; Mihovilovic, M. D.; Stanetty, P. *Lett. Org. Chem.* **2009**, *6*, 171; (b) Stanetty, P.; Schnürch, M.; Mereiter, K.; Mihovilovic, M. D. *J. Org. Chem.* **2005**, *70*, 567.
18. (a) Hartwig, J. F. *Angew. Chem., Int. Ed.* **1998**, *37*, 2046; (b) Paul, F.; Patt, J.; Hartwig, J. F. *J. Am. Chem. Soc.* **1994**, *116*, 5969; (c) Hill, L. L.; Moore, L. R.; Huang, R.; Craciun, R.; Vincent, A. J.; Dixon, D. A.; Chou, J.; Woltermann, C. J.; Shaughnessy, K. H. *J. Org. Chem.* **2006**, *71*, 5117; (d) Yin, J.; Zhao Matthew, M.; Huffman Mark, A.; McNamara James, M. *Org. Lett.* **2002**, *4*, 3481; (e) Wolfe, J. P.; Buchwald, S. L. *J. Org. Chem.* **2000**, *65*, 1144; (f) Doherty, S.; Knight, J. G.; Smyth, C. H.; Sore, N. T.; Rath, R. K.; McFarlane, W.; Harrington, R. W.; Clegg, W. *Organometallics* **2006**, *25*, 4341; (g) Liu, Y.; Bai, Y.; Zhang, J.; Li, Y.; Jiao, J.; Qi, X. *Eur. J. Org. Chem.* **2007**, 6084; (h) Lipshutz, B. H.; Nihan, D. M.; Vinogradova, E.; Taft, B. R.; Boskovic, Z. V. *Org. Lett.* **2008**, *10*, 4279.
19. General procedure for nucleophilic substitution reactions towards compounds **3**–**12**: 1.0 equiv of the halothiazole, 1.5 equiv of the amino-substrate and 0.5 equiv of *p*-toluenesulfonic acid were dissolved in *i*-propanol and the reaction mixture was stirred at 80 °C until the reaction was complete (TLC). The reaction mixture was then diluted with ethyl acetate and washed with saturated $NaHCO_3$ solution and brine followed by general work-up. Purification was carried out by Kugelrohr distillation.
20. (a) Parisien, M.; Valette, D.; Fagnou, K. *J. Org. Chem.* **2005**, *70*, 7578; (b) Liegault, B.; Lapointe, D.; Caron, L.; Vlassova, A.; Fagnou, K. *J. Org. Chem.* **2009**, *74*, 1826.
21. Primas, N.; Bouillon, A.; Lancelot, J.-C.; El-Kashef, H.; Rault, S. *Tetrahedron* **2009**, *65*, 5739.
22. Miyaoku, T.; Mori, A. *Heterocycles* **2009**, *77*, 151.
23. (a) Roger, J.; Pozgan, F.; Doucet, H. *J. Org. Chem.* **2009**, *74*, 1179; (b) Pozgan, F.; Roger, J.; Doucet, H. *ChemSusChem* **2008**, *1*, 404.
24. Greene, T. W. W., 3rd ed. In *Protective groups in Organic Synthesis*; Wiley-Interscience, 1999.
25. *N-Benzyl-N-phenylthiazoleamine* **13**: *N*-Phenylthiazoleamine **3** (30 mg, 0.17 mmol. 1.0 equiv), benzyl bromide (38 mg, 0.22 mmol, 1.3 equiv), and NaH (4.1 mg, 0.17 mmol, 1.0 equiv) were dissolved in dry dimethylformamide (2 mL) and stirred at room temperature for 5 h. The reaction mixture was diluted with ethyl acetate, silica gel was added, and this suspension was concentrated in vacuo, followed by MPLC purification (light petroleum/ethyl acetate 85:15 + 5% of triethylamine). Compound **13** was obtained as a beige solid (30 mg, 66%). Mp: 79–80 °C; R_f (light petroleum/ethyl acetate 5:2) 0.20; ^{1}H NMR (200 MHz, $CDC1_3$) δ = 5.12 (s, 2H), 6.40 (d, J = 3.7 Hz), 7.15–7.33 (m, 10H); ^{13}C NMR (50 MHz, $CDC1_3$) δ = 56.6 (t), 107.7 (d), 126.2 (d), 126.8 (d), 127.2 (d), 127.7 (d), 128.5 (d), 129.8 (d), 137.7 (s), 139.3 (d), 145.3 (s), 170.9 (s); HRMS: MH+, found 267.0955. $C_{16}H_{14}N_2S$ requires 267.0950.
26. *N-(3-Benzylthiazol-2(3H)-ylidene)aniline* **14**: *N*-Phenylthiazoleamine **3** (264 mg, 1.50 mmol, 1.0 equiv.), benzyl bromide (334 mg, 1.96 mmol, 1.3 equiv), and triethylamine (152 mg, 1.50 mmol, 1.0 equiv) were dissolved in dry dioxane (4 mL) at 0 °C. The reaction mixture was slowly warmed to room temperature before it was heated to 120 °C for 3 days. The mixture was then diluted with ethyl acetate, silica gel was added, and this suspension was concentrated in vacuo, followed by MPLC purification (light petroleum/ethyl acetate 85:15 + 4% of triethylamine). Compound **14** was obtained as a light yellow solid (287 mg, 72%). Mp: 94–95 °C; R_f (light petroleum/ethyl acetate 5:2) 0.20; ^{1}H NMR (200 MHz, $CDC1_3$) δ = 5.06 (s, 2H), 5.85 (d, J = 4.9 Hz, 1H), 6.50 (d, J = 4.9 Hz, 1H), 7.00–7.10 (m, 3H), 7.33–7.37 (m, 7H); ^{13}C NMR (50 MHz $CDCl_3$) δ = 49.8 (t), 97.6 (d), 121.4 (d), 123.2 (d), 126.3 (s), 128.1 (s), 128.6 (d), 129.4 (d), 136.8 (s); HRMS: MH+, found 267.0954. $C_{16}H_{14}N_2S$ requires 267.0950.
27. (a) Oegretir, C.; Demirayak, S.; Tay, N. F.; Duran, M. *J. Chem. Eng. Data* **2008**, *53*, 422; (b) Mohamed, A. A.; El-Harby, A. W. *Theochem* **2007**, *817*, 125; (c) Mohamed, A. A.; El-Harby, A. W. *Theochem* **2008**, *849*, 52; (d) Zeng, Y.; Ren, Y. *Int. J. Quantum Chem.* **2006**, *107*, 247; (e) Remko, M.; Swart, M.; Bickelhaupt, F. M. *Bioorg. Med. Chem.* **2006**, *14*, 1715.
28. *General procedure for direct arylation reactions towards compounds* **15**–**24**: 1.0 equiv of **3**, 2.0 equiv of the halo-component, 2.0 equiv of KOAc, and 0.01 equiv of $Pd(OAc)_2$ were charged into the reaction vessel in that same order. Dimethylacetamide was added and the reaction vial was evacuated and purged with argon three times. The reaction mixture was then stirred at 120 °C until the reaction was complete. The solution was diluted with ethyl acetate, silica gel was added, and this mixture was concentrated in vacuo, followed by MPLC purification.
29. (a) Hansen, J. M.; Klass, M.; Harris, C.; Csete, M. *Cell Biol. Int.* **2007**, *31*, 546; (b) Chen, S. E.; Jin, B.; Li, Y. P. *Am. J. Physiol. Cell Physiol.* **2007**, *292*, C1660; (c) Li, Y.; Li, J.; Zhu, J.; Sun, B.; Branca, M.; Tang, Y.; Foster, W.; Xiao, X.; Huard, J. *Mol. Ther.* **2007**, *15*, 1616.
30. Zebedin, E.; Sandtner, W.; Galler, S.; Szendroedi, J.; Just, H.; Todt, H.; Hilber, K. *Am. J. Physiol. Cell Physiol.* **2004**, *287*, C270.
31. (a) Nguyen, T. H.; Bertrand, M. J.; Sterpin, C.; Achouri, Y.; De Backer, O. R. *BMC Cell Biol.* **2010**, *11*, 57; (b) Deponti, D.; François, S.; Baesso, S.; Sciorati, C.; Innocenzi, A.; Broccoli, V.; Muscatelli, F.; Meneveri, R.; Clementi, E.; Cossu, G.; Brunelli, S. *J. Cell Biol.* **2007**, *179*, 305.