DOI: 10.1002/adsc.201600748
Advanced Synthesis & Catalysis

Copper-Catalyzed Domino Reaction Involving Nitro as an Unexpected Leaving Group: Construction of Dibenzo-Fused Azepinone Ring

Rajnikanth Sunke,[a] E. V. Venkat Shivaji Ramarao,[a] Suresh Babu Nallapati,[a] Raghavender Medisetti,[a] Pushkar Kulkarni,[a] Ravi Kumar Kapavarapu,[b] Ramudu Bankala,[a] Kishore V. L. Parsa,[a] and Manojit Pal[a,*]

[a] Dr. Reddy's Institute of Life Sciences, University of Hyderabad Campus, Gachibowli, Hyderabad – 500 046, India
E-mail: manojitpal@rediffmail.com
[b] Doctoral Programme in Experimental Biology and Biomedicine, Center for Neuroscience and Cell Biology, University of Coimbra, 3004-517 Coimbra, Portugal

Received: July 12, 2016; Revised: August 9, 2016; Published online: ■■ ■■, 0000

Supporting information for this article can be found under: http://dx.doi.org/10.1002/adsc.201600748.

Abstract: A copper-catalyzed new domino reaction allowed the facile and direct construction of the dibenzo-fused azepinone ring leading to an array of novel small molecules. The co-catalyst, ligand or additive free one-pot method afforded a unique class of functionalized derivatives, one of which showed encouraging PDE4 inhibition *in vitro* and apoptosis *in vivo*.

Keywords: azepinones; catalysis; copper; domino reaction; PDE4

New synthetic methodologies that can provide access to diversity-based uncommon nitrogen heterocycles are of high demand whereby metal-catalyzed cascade/domino reactions have to date occupied the center stage. Indeed, the development of simpler but innovative methodologies is a focus of current research.

The dibenzo-fused 7-membered nitrogen heterocycles such as oxazepinones, diazepinones and azepinones are of particular interest.[1] Compounds containing the 5*H*-dibenzo[*b*,*e*]azepin-6(11*H*)-one framework have been explored as histone deacetylase (HDAC) inhibitors,[2a] or chemokine receptor antagonists[2b,c] for the treatment of cancer and modulators of the multidrug resistance phenotype.[2d] This framework attracted our attention due to the exploration of related compounds (e.g., **A**, Figure 1) as CCR1 receptor antagonists for the treatment of chronic inflammatory diseases such as multiple sclerosis and rheumatoid arthritis.[3] Notably, inhibitors of PDE4 (e.g., **B**, Figure 1),[4] reported to be useful for the treatment of these diseases too, appeared to have structural relevance with **A** particularly with respect to the CN substituted cycloalkyl ring (arguably essential for PDE4 inhibition in addition to the amidic NH).[4b] This prompted us to explore compound **C** (Figure 1) as potential inhibitor of PDE4. Our prediction was further supported by docking[5] of a representative compound **D** (Figure 1) into PDE4B *in silico* (Figure 2) that showed H-bonding interaction between the NH of **D** and the MET431 residue of PDE4B with a docking score of $-66.28\ \text{kcal mol}^{-1}$ comparable to that of the reference standard rolipram, $-59.35\ \text{kcal mol}^{-1}$. Thus a straightforward synthetic method leading to **C** was needed. While a number of syntheses of 5*H*-dibenzo[*b*,*e*]azepin-6(11*H*)-ones have been reported[6] only few are known for their 11-cyano derivatives.[2d,3] Al-

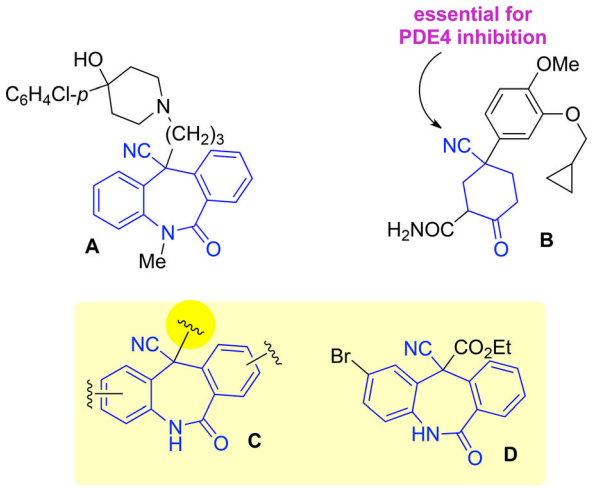


Figure 1. Design of **C** (and **D**) based on reported molecules **A/B**.[3,4]

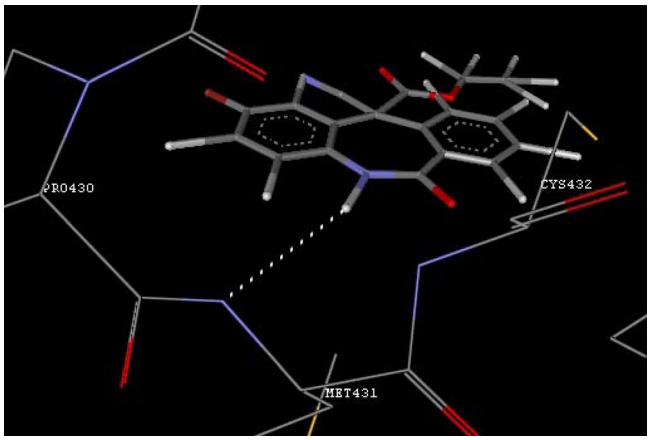
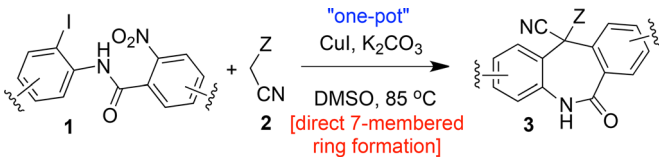


Figure 2. Docking of compound **D** into PDE4B (PDB ID: 1XMY).

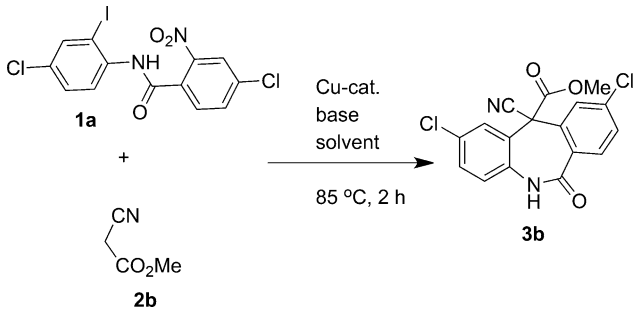
though effective for the synthesis of specific compounds, these methods involve lengthy steps and appeared to be not suitable for the direct synthesis of **C**. Accordingly, we have developed a co-catalyst, ligand or additive free one-pot synthesis of **C** (or **3**, Scheme 1) *via* a new and versatile Cu-catalyzed domino reaction involving NO_2 as an unexpected leaving group. The preliminary results of this study along with a pharmacological evaluation of the newly synthesized compounds are presented. Notably, Cu-mediated domino reactions[7] and the use of the NO_2 group[8] in organic synthesis have been studied earlier. While Cu-mediated displacement of the NO_2 group by an S-nucleophile[9] has been reported once but none is known involving a C-nucleophile.

The key starting material **1** was prepared *via* amide bond formation between 2-nitroaryl carboxylic acid chloride and 2-iodoanilines (see the Supporting Information). Then the Cu-catalyzed coupling of iodo compound **1a** with methyl cyanoacetate (**2b**) was examined under various conditions (Table 1). Initially, we expected the formation and isolation of a normal Ullmann coupled product **4** (Scheme 2) that could be converted to the target compound **3b** *via* a number of steps, for example, converting its NO_2 group to iodo (*via* reduction followed by Sandmeyer reaction) and then a second Ullmann type coupling in an intramolecular fashion. To our surprise the coupling of **1a** with **2b** afforded **3b** directly as the only product. We were delighted with this observation and continued our study. To identify the best reaction conditions



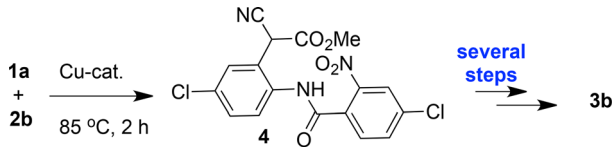
Scheme 1. Synthesis of **3** *via* a Cu-catalyzed domino reaction.

Table 1. Effect of conditions on domino reaction of **1a** with **2b**.[a]



Entry	Catalyst	Base	Solvent	Yield[b] [%]
1	CuI	K_2CO_3	DMSO	94 (65, 37)[c]
2	CuI	Cs_2CO_3	DMSO	87
3	CuI	Na_2CO_3	DMSO	90
4	CuI	K_3PO_4	DMSO	66
5	CuI	K_2CO_3	DMF	82
6	CuI	K_2CO_3	1,4-dioxane	0
7	CuI	K_2CO_3	toluene	0
8	CuBr	K_2CO_3	DMSO	83
9	CuCl	K_2CO_3	DMSO	64
10	No Cat.	K_2CO_3	DMSO	0

[a] Reactions are carried out using **1a** (1 mmol), **2b** (1.2 mmol), catalyst (0.1 mmol), and a base (3 mmol) in a solvent (2.5 mL) at 85 °C under open air.
[b] Isolated yield.
[c] 0.05 and 0.02 mmol of CuI used.

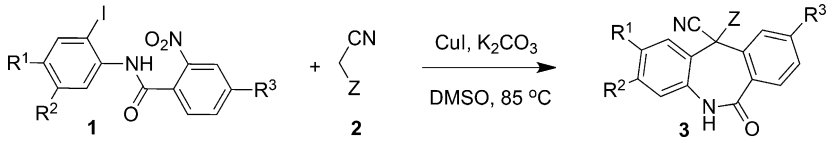


Scheme 2. Planned/expected reactions/steps leading to **3b**.

a range of bases, for example, K_2CO_3, Na_2CO_3, Cs_2CO_3 and K_3PO_4 (entries 1–4, Table 1), solvents, for example, DMSO, DMF, 1,4-dioxane and toluene (entries 1 and 5–7, Table 1) and catalysts, for example, CuI, CuBr and CuCl (entries 1, 8 and 9, Table 1) were assessed. Accordingly, a combination of CuI and K_2CO_3 in DMSO was found to be optimal. Notably, a decrease in product yield or no reaction was observed when a decreased amount of CuI or no CuI was used (entries 1 and 10, Table 1) indicating the key role played by the catalyst.

The scope of the present Cu-catalyzed domino reaction was then examined which afforded compound **3** with a variety of substitution patterns (Table 2). The reaction proceeded well with various substituents on **1**. For example, for R^1, R^2 and R^3 selected from H, F, Cl, Br or Me the corresponding product was isolated in good yield. Similarly, the use of nitriles (**2a**–**d**) containing a CO_2Me, CO_2Et, $PO(OEt)_2$ or CN moiety

Table 2. Cu-catalyzed synthesis of 11-cyano 5*H*-dibenzo[*b*,*e*]azepin-6(11*H*)-ones **3**[a] (see also Table S-1 in the Supporting Information).

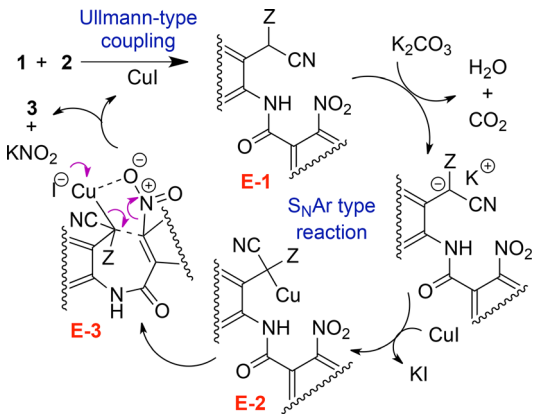


Entry	*o*-Iodo amide (**1**): R^1, R^2, R^3	Nitrile (**2**): Z	Time [h]	Product (**3**): R^1, R^2, R^3, Z	Yield[b] [%]
1	**1a:**Cl, H, Cl	**2a:** CO_2Et	2	**3a:** Cl, H, Cl, CO_2Et	91
2	**1a**	**2b:** CO_2Me	2	**3b:** Cl, H, Cl, CO_2Me	94
3	**1b:** Cl, H, F	**2a**	2	**3c:** Cl, H, F, CO_2Et	90
4	**1c:** F, H, F	**2a**	2.5	**3d:** F, H, F, CO_2Et	89
5	**1c**	**2b**	2	**3e:** F, H, F, CO_2Me	92
6	**1c**	**2c:** $PO(OEt)_2$	2.5	**3f:** F, H, F, $PO(OEt)_2$	41
7	**1d:** F, H, Cl	**2b**	2	**3g:** F, H, Cl, CO_2Me	88
8	**1e:** Me, H, Cl	**2a**	2	**3h:** Me, H, Cl, CO_2Et	93
9	**1e**	**2b**	2	**3i:** Me, H, Cl, CO_2Me	91
10	**1f:** Me, Me, H	**2b**	2	**3j:** Me, Me, H, CO_2Me	86
11	**1g:** Cl, H, H	**2a**	2	**3k:** Cl, H, H, CO_2Et	82
12	**1h:** F, H, H	**2a**	2	**3l:** F, H, H, CO_2Et	79
13	**1h**	**2b**	2	**3m:** F, H, H, CO_2Me	85
14	**1i:** Br, H, H	**2a**	2.5	**3n:** Br, H, H, CO_2Et	76
15	**1j:** Me, H, H	**2a**	2	**3o:** Me, H, H, CO_2Et	94
16	**1j**	**2b**	2	**3p:** Me, H, H, CO_2Me	87
17	**1k:** H, H, H	**2a**	2.5	**3q:** H, H, H, CO_2Et	79
18	**1k**	**2b**	2.5	**3r:** H, H, H, CO_2Me	77
19	**1l:** H, Me, H	**2d:** CN	6	**3s:** H, Me, H, CN	52
20	**1j**	**2d**	6	**3t:** Me, H, H, CN	47
21	**1i**	**2d**	6	**3u:** Br, H, H, CN	45

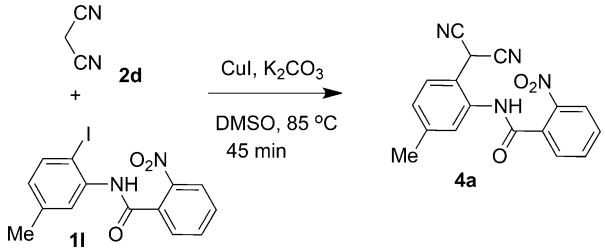
[a] All the reactions are carried out using compound **1** (1 mmol), **2** (1.2 mmol), K_2CO_3 (3.0 mmol) and 10 mol% CuI in DMSO (5 mL) under open air.
[b] Isolated yield.

was successful. All the functionalized compounds synthesized were characterized by spectral (^{1}H and ^{13}C NMR, MS and HPLC) data (see the Supporting Information) for example, (i) a ^{1}H NNMR signal near δ = 11.5 (D_2O exchangable) due to -NH-, and δ = 4.0 due to ester-OMe or δ = 4.42 and 1.40 due to ester-OEt, (ii) ^{13}C NMR signals near 165 and 169 ppm due to ester and amide C=O, respectively, confirmed the presence of these functional groups. Furthermore, DEPT ^{13}C NMR sepctra of a representative compound **3o** indicated the presence of nine quaternary carbons and one -CH_2- group.

Mechanistically, the reaction seemed to proceed *via* a Cu-catalyzed Ullmann type C–C bond formation between the iodo compound **1** and nitrile **2** to give the C-arylated nitrile intermediate **E-1** *in situ* (Scheme 3). On subsequent deprotonation followed by reaction with CuI, **E-1** affords an organo-Cu species **E-2**. An intramolecular interaction between the Cu moiety and the NO_2 group causes polarization of the C–NO_2 bond, for example, **E-3** that facilitates a nucleophilic attack on the NO_2 bearing aromatic carbon by the proximate Cu-coordinated benzylic carbanion in an intramolecular fashion. Thus the product **3** is formed *via* an intramolecular displacement of NO_2 group (S_NAr type reaction) with the regeneration of catalyst CuI. The intermediacy of **E-1** was further supported by the isolation of compound **4a** from the reaction of **1l** with **2d** after 45 min (Scheme 4) which, on further continuation of reaction, was converted to **3s** (Table 2) in 48% yield [for example, **4a** (1.0 mmol), K_2CO_3 (3.0 mmol) and 10 mol% CuI in DMSO (5 mL) at 85 °C for 4 h under open air]. To assess the role of the Cu catalyst in the



Scheme 3. The proposed reaction mechanism.



Scheme 4. Preparation of compound **4a**.

transformation of **E-1** to azepinone **3** (Scheme 3) a control reaction was performed using the isolated intermediate **4a** in the absence of Cu catalyst [for example, **4a** (1.0 mmol) and K_2CO_3 (2.0 mmol) in DMSO (5 mL) at 85 °C for 4 h under open air]. The isolation of the corresponding product **3s** in poor yield (11%) indicated the key role played by the Cu catalyst in this transformation.

In an enzyme-based *in vitro* assay[10] two of the synthesized compounds showed good inhibition of PDE4B [for example, **3o** (70%) and **3n** (64%)] when tested at 10 μM (see the Supporting Information) with rolipram (85% inhibition at 10 μM) as a reference standard. Compound **3o** showed dose-dependent inhibition of PDE4B (Figure 3). The enzyme–compound interaction was further supported by the docking[5] results of **3o** (see the Supporting Information) with PDE4B protein (docking score −66.28 kcal mol^{-1}). The amidic NH of the central ring of **3o** participated in H-bonding with the MET431 residue of PDE4B. In view of the fact that the PDE4 inhibitor rolipram induced apoptosis in B-CLL cells[11] the compound **3o** was tested for its apoptotic activities in Zebrafish embryos[12a,b] at 1, 3, 10 and 30 μM along with a known drug methotrexate[12c] at 30 μM. The compound **3o** showed considerable apoptotic effects (Figure 4 and Figure 5) with $EC_{50} \approx 30$ μM and therefore is of further interest as a preliminary hit molecule. Indeed, **3o** is the first example of a 5*H*-diben-

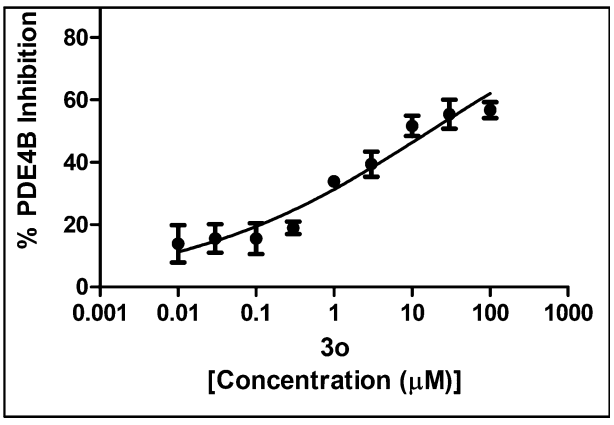


Figure 3. Dose-dependent inhibition of PDE4B by compound **3o**.

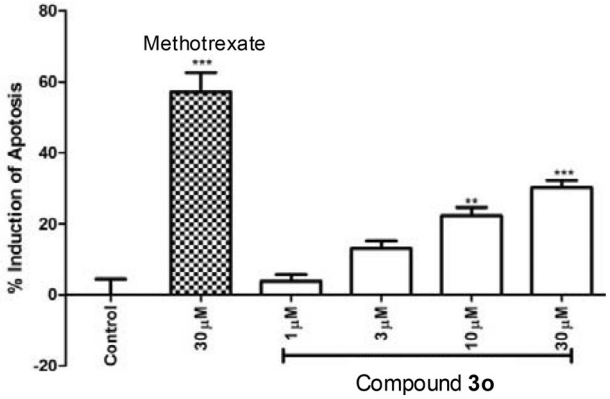


Figure 4. The percentage induction of apoptosis caused by compound **3o** at different concentrations along with methotrexate. All the statistical analysis was performed using GraphPad Prism® software.

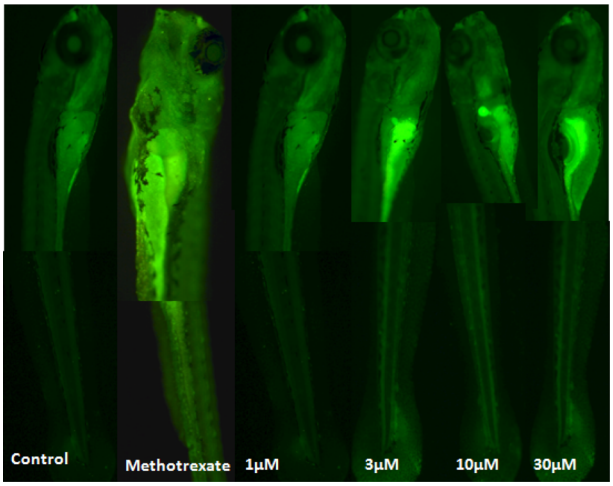


Figure 5. Representative images of the embryos treated with methotrexate (30 μM) and compound **3o** (1, 3, 10 and 30 μM) assayed for apoptosis. Only the selected parts of embryos are shown.

zo[*b*,*e*]azepin-6(11*H*)-one-based PDE4 inhibitor/apoptotic agent.

In conclusion, a Cu-catalyzed straightforward and inexpensive yet innovative method has been developed for rapid access to a library of small molecules based on the dibenzo-fused azepinone framework. This operationally simple one-pot methodology involves 7-membered ring formation *via* Ullmann type C–C coupling followed by an unusual intramolecular displacement of an NO_2 group. One of the synthesized compounds showed encouraging PDE4 inhibition *in vitro/in silico* and apoptosis *in vivo* indicating dibenzo-fused azepinone as a new pharmacophore for PDE4 inhibition/apoptosis. Overall, our findings related to dibenzo-fused azepinone are unprecedented and could be a useful addition to the chemistry and pharmacology of this class of nitrogen heterocycle.

Experimental Section

Typical Procedure for Preparation of Compound 3a

A mixture of 4-chloro-*N*-(4-chloro-2-iodophenyl)-2-nitrobenzamide (**1a)** (0.24 mmol), K_2CO_3 (0.74 mmol), methyl 2-cyanoacetate (**2b**) (0.29 mmol) and CuI (0.024 mmol) in DMSO (2 mL) was heated at 85 °C under the open air for 2 h. After completion of the reaction, the mixture was cooled to room temperature, diluted with ethyl acetate (15 mL) and passed through celite. The filtrate was collected, washed with water (3 × 15 mL) followed by brine solution (25 mL), dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by column chromatography using ethyl acetate-hexane to give the desired product **3a**.

Acknowledgements

RS thank CSIR, for a research fellowship. The authors thank DBT, India (Grant BT/PR4286/BRB/10/1012/2011) for support.

References

[1] a) For HIV-1 reverse transcriptase inhibitory properties of dipyridodiazepinones, pyridobenzoxazepinones and dibenzoxazepinones, see: J. M. Klunder, K. D. Hargrave, M. West, E. Cullen, K. Pal, M. L. Behnke, S. R. Kapadia, D. W. McNeil, J. C. Wu, G. C. Chow, J. Adams, *J. Med. Chem.* **1992**, *35*, 1887; b) for antiarrhythmic defibrillatory activity of dibenzo[*b,e*][1,4]diazepin-11-one and dibenzo[*b,e*][1,4]diazepine derivatives, see: O. Levy, M. Erez, D. Varon, E. Keinan, *Bioorg. Med. Chem. Lett.* **2001**, *11*, 2921.

[2] a) M. Bigioni, A. Ettorre, P. Felicetti, S. Mauro, C. Rossi, C. A. Maggi, E. Marastoni, M. Binaschi, M. Parlani, D. Fattori, *Bioorg. Med. Chem. Lett.* **2012**, ***22***, 5360; b) W. Newman, C. F. Schwender, C. R. Mackay, J. C. Pinto, *World Patent Application No.* WO1999/37617 A1, **1999**; c) J. R. Luly, Y. Nakasato, E. Ohshima H. Sone, O. Kotera, G. C. B. Harriman, K. G. Carson, *World Patent Application No.* WO2001/9094 A2, **2001**; d) A. Dhainaut, G. Regnier, G. Atassi, A. Pierre, S. Leonce, L. Kraus-Berthier, J. F. Prost, *J. Med. Chem.* **1992**, *35*, 2481.

[3] H. P. Ng, M. Karen, J. G. Bauman, A. Ghannam, I. Islam, M. Liang, R. Horuk, J. Hesselgesser, R. M. Snider, H. D. Perez, M. M. Morrissey, *J. Med. Chem.* **1999**, *42*, 4680.

[4] a) S. B. Christensen, P. E. Bender, C. J. Forster, *U.S. Patent Application* US 5,811,455, **1998**; b) for s similar class of compounds, see: A. Kodimuthali, S. S. L. Jabaris, M. Pal, *J. Med. Chem.* **2008**, *51*, 5471.

[5] a) The molecular docking simulations were carried out using the GRIP method of docking in Biopredicta module of Vlife MDS (Molecular Design Suite) 4.6. (for detailed procedure, see the Supporting Information); b) G. L. Card, B. P. England, Y. Suzuki, D. Fong, B. Powell, B. Lee, C. Luu, M. Tabrizizad, S. Gillette, P. N. Ibrahim, D. R. Artis, G. Bollag, M. V. Milburn, S. H. Kim, J. Schlessinger, K. Y. Zhang, *Structure* **2004**, *12*, 2233.

[6] a) R. A. Bunce, J. E. Schammerhorn, *J. Heterocycl. Chem.* **2006**, *43*, 1031; b) J. Irurre, F. Marquillas, A. Alvarez-Larena, J. F. Piniella, *Can. J. Chem.* **1994**, *72*, 33; c) A. K. Sinha, S. Nizamuddin, *Indian J. Chem. Sec B:* **1984**, *23*, 165; d) A. Fecher, H. Fretz, K. Hilpert, M. Riederer, *World Patent Application No* WO2005/94816 A1, **2005**.

[7] For selected Cu-mediated domino reaction, see: a) M. Jiang, J. Li, F. Wang, Y. Zhao, X. Dong, W. Zhao, *Org. Lett.* **2012**, *14*, 1420; b) T. Liu, C. Zhu, H. Yang, H. Fu, *Adv. Synth. Catal.* **2012**, *354*, 1579; c) J. Lu, X. Gong, H. Yang, H. Fu, *Chem. Commun.* **2010**, *46*, 4172; d) V. A. Vaillard, R. A. Rosi, S. E. Martin, *Org. Biomol. Chem.* **2011**, *9*, 4927; e) B. Zou, Q. Yuan, D. Ma, *Angew. Chem.* **2007**, *119*, 2652; *Angew. Chem. Int. Ed.* **2007**, *46*, 2598.

[8] <For very recent and selected examples on the use of the nitro group in organic synthesis, see: a) K. Bera, N. S. Satam, I. N. N. Namboothiri, *J. Org. Chem.* **2016**, *81*, 5670; b) T. Kumar, N. S. Satam, I. N. N. Namboothiri, *Eur. J. Org. Chem.* **2016**, 3316; c) P. Basu, P. Prakash, E. Gravel, N. Shah, K. Bera, E. Doris, I. N. N. Namboothiri, *ChemCatChem* **2016**, *8*, 1298; d) V. Mane, J. Pandey, N. Ayyagari, C. Dey, R. Kale, I. N. N. Namboothiri, *Org. Biomol. Chem.* **2016**, *14*, 2427.

[9] For a Cu-mediated displacement of the NO_2 group by a thiol reactant, see: S. S. Bahekar, A. P. Sarkate, V. M. Wadhai, P. S. Wakte, D. B. Shinde, *Catal. Commun.* **2013**, *41*, 123.

[10] P. Wang, J. G. Myers, P. Wu, B. Cheewatrakoolpong, R. W. Egan, M. M. Billah, *Biochem. Biophys. Res. Commun.* **1997**, *234*, 320.

[11] a) B. Siegmund, J. Welsch, F. Loher, *Leukemia* **2001**, *15*, 1564. b) In addition to inducing apoptosis, inhibition of PDE4 has also been reported to induce growth suppression, glucocorticoid sensitivity, p53, and p21(WAF1/CIP1) proteins in human acute lymphoblastic leukemia cells; see: R. Ogawa, M. B. Streiff, A. Bugayenko, G. J. Kato, *Blood* **2002**, *99*, 3390.

[12] Pharmacological effects of small molecules in early development can be assessed in embryos of zebrafish *Danio rerio* that are considered as excellent animal models for such a study. This allows effective *in vivo* evaluations of potential drugs before embarking on expensive studies in mice and higher animals. a) M. Westerfield, *The Zebrafish Book. a Guide for the Laboratory Use of Zebrafish (Danio rerio)*, 4th edn., University of Oregon Press, Eugene, OR, **2000**; b) A. Nakhi, S. Archana, G. P. Seerapu, K. S. Chennubhotla, K. L. Kumar, P. Kulkarni, D. Haldar, M. Pal, *Chem. Commun.* **2013**, *49*, 6268; c) J. A. Ellard, *U.S. Patent Application No.* US 4,080,325 A, **1978**.