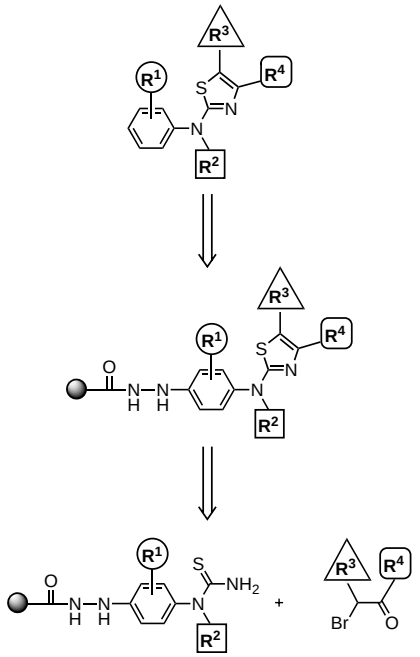
Traceless Solid-Phase Synthesis of 2-Aminothiazoles: Receptor Tyrosine Kinase Inhibitors with Dual Selectivity for Tie-2 and VEGFR-2**

Frank Stieber, Ralph Mazitschek, Natascha Soric, Athanassios Giannis,* and Herbert Waldmann*

Paramount to success in the combinatorial and parallel synthesis of compound libraries on polymeric supports is the proper choice of the molecular scaffolds onto which different functional groups are grafted, the development of reliable multistep sequences on the polymeric support including widely differing types of transformations, and the use of linker groups that guarantee release of the target compounds from the solid support under the mildest conditions. Ideally, a linker should release the products while forming a C–H bond in place of the resin attachment, thus leaving behind no trace of a solid-phase synthesis ("traceless linker").[1,2]

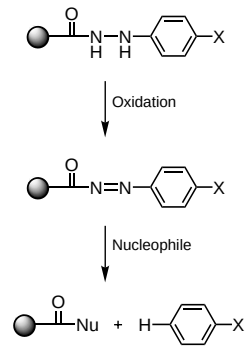
2-Aminothiazoles have recently found application in drug development for the treatment of allergies,[3] hypertension,[4] inflammation,[5] schizophrenia,[6] bacterial[7] and HIV infections,[8] and very recently for the treatment of pain,[9] as fibrinogen receptor antagonists with anti-thrombotic activity,[10] as new inhibitors of bacterial DNA gyrase B,[11] and in the development of cyclin-dependent kinase (CDK) inhibitors.[12]

Here we describe a new and efficient method for the solid-phase synthesis[13] of 2-aminothiazoles that employs the traceless hydrazide linker[14] and report the biological investigation of the library. The Hantzsch synthesis was employed as the key step (Scheme 1) for the solid-phase synthesis of the 2-aminothiazole core. We intended to generate the intermediary thioureas from polymer-bound anilines by treatment with an N-protected isothiocyanate. The *para*-position to the aniline amino group was chosen as the attachment point for the traceless hydrazide linker. Traceless cleavage of the linker is achieved by oxidation of the phenylhydrazide to the acyldiazene and subsequent nucleophilic attack on the carbonyl group (Scheme 2).



Scheme 1. Plan for the traceless solid-phase synthesis of the 2-aminothiazoles.

Amino-functionalized polystyrene **1** (1.3 mmol g^{-1}) was coupled with monomethyl adipicate (**2**) to yield the corresponding polymer-bound amide, and the methyl ester was saponified by treatment with LiOH (Scheme 3). This two-step sequence proceeds with an overall yield of 93–98%.[15] The resulting acid-functionalized resin **3** was then converted into the *p*-nitrophenylhydrazides **5** by activation with *N*,*N*-diisopropylcarbodiimide (DIC) and *N*-hydroxybenzotriazole (HOBt) and treatment with differently substituted 4-nitrophenylhydrazines **4**. Prior to the planned reduction of the nitrobenzene groups to the anilines the two hydrazide nitrogen atoms were acylated with Fmoc-Cl (Fmoc = fluorenylmethoxycarbonyl) to avoid problems in a subsequent step employing Fmoc-isothiocyanate **9** (see below). Reduction of the nitro group to the amino function proceeded quantitatively if $SnCl_2$[16a] was employed in DMF as solvent[16b,c] (determined by GC-MS).



Scheme 2. Principle of the oxidative cleavage of the hydrazide linker.

The use of polymer-bound anilines **6** in the subsequent synthesis sequence leads to the formation of N-monosubstituted 2-aminothiazoles. To also get access to the N,N-disubstituted heterocycles N-functionalization of the amines

[*] Prof. Dr. A. Giannis
Institut für Organische Chemie
Universität Leipzig
Johannisallee 29, 04103 Leipzig (Germany)
Fax: (+49) 341-9736-599
E-mail: giannis@chemie.uni-leipzig.de
Prof. Dr. H. Waldmann, Dr. F. Stieber
Max-Planck-Institut für molekulare Physiologie
Abteilung Chemische Biologie
Otto-Hahn-Strasse 11, 44227 Dortmund (Germany)
Fax: (+49) 231-133-2499
E-mail: herbert.waldmann@mpi-dortmund.mpg.de
and
Universität Dortmund
Fachbereich 3, Organische Chemie
44221 Dortmund (Germany)
Dr. F. Stieber
Semaia Pharmaceuticals GmbH&Co.KG
Emil-Figge-Strasse 76a, 44227 Dortmund (Germany)
Dr. R. Mazitschek, Dipl.-Chem. N. Soric
Institut für Organische Chemie
Universität Karlsruhe
Richard-Willstätter-Allee 2, 76128 Karlsruhe (Germany)

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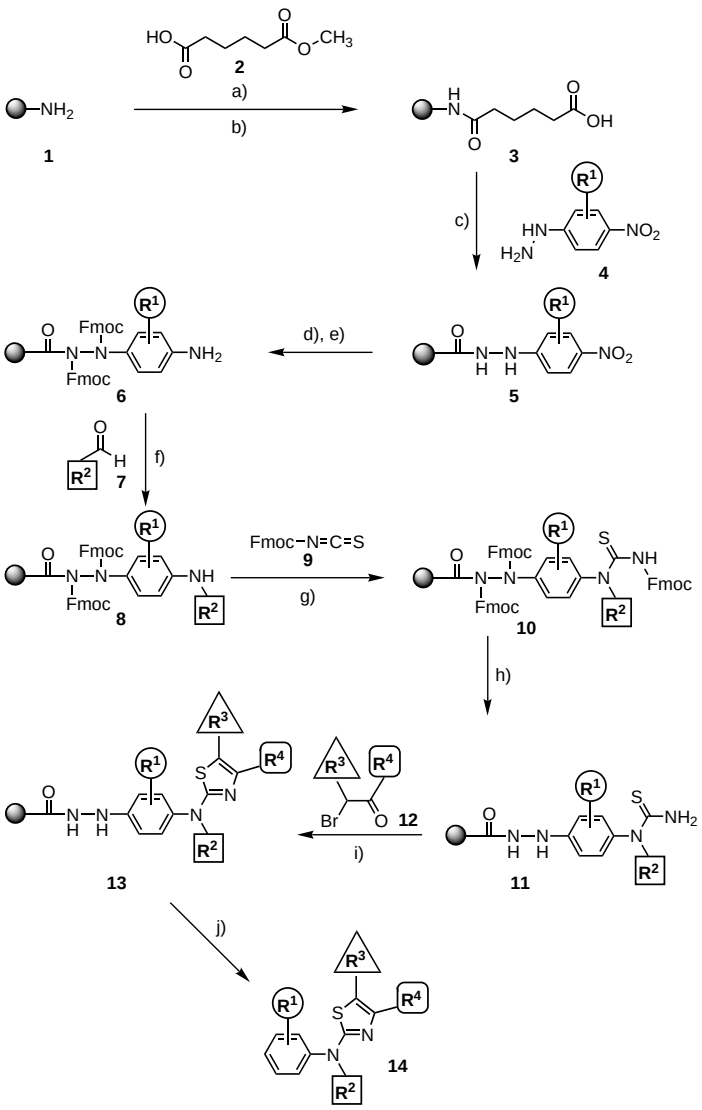

Scheme 3. Traceless solid-phase synthesis of 2-aminothiazoles **14**. a) 3 equiv **2**, 3 equiv DIC, 3 equiv HOBt, 3 equiv NEt_3, CH_2Cl_2, room temperature, 18 h; b) THF/1 % LiOH in H_2O (1:1), room temperature, 24 h; c) 3 equiv **4**, 3 equiv DIC, 3 equiv HOBt, 3 equiv NEt_3, CH_2Cl_2, room temperature, 18 h; d) 10 equiv Fmoc-Cl, pyridine, CH_2Cl_2, 15 h; e) 2 M $SnCl_2 \cdot 2H_2O$, DMF, room temperature, 18 h; f) 10 equiv aldehyde **7**, THF, HOAc, room temperature, 1 h, wash, then 10 equiv $NaCNBH_3$, THF/HOAc, room temperature, 15 h; g) 3 equiv Fmoc-NCS **9**, CH_2Cl_2, pyridine, room temperature, 15 h; h) DMF/piperidine 4:1, room temperature, 2 × 5 min; i) 0.1 M solution of **12** in dioxane, room temperature, 2 × 3 h; j) 0.5 equiv $Cu(OAc)_2$, *n*-propylamine, O_2, room temperature, 2 h, then solid-phase extraction.

6 by means of reductive amination was investigated. Although this type of transformation is well-established in solid-phase synthesis, its application to anilines **6** turned out to be unexpectedly difficult. After substantial experimentation it was found that quantitative conversion was achieved if 10 equivalents of aldehyde and $NaCNBH_3$ were employed in THF/AcOH (100:1).[17] However, under these conditions formation of the tertiary amine due to double reductive alkylation was also observed. This problem was overcome by separating imine formation and reduction into two individual steps.

Anilines **8** were converted efficiently to the corresponding thioureas **11** by treatment with Fmoc-NCS (**9**)[13b] and subsequent removal of all three Fmoc groups present in intermediates **10** with piperidine in DMF. With polymer-bound thioureas **11** in hand we investigated the Hantzsch thiazole synthesis on the polymeric support. Gratifyingly, the desired 2-aminothiazoles were formed smoothly upon two successive treatments with 0.1 M solutions of different α-bromocarbonyl compounds **12** in dioxane (Scheme 3). Finally, the target compounds **14** were released from the solid support by treatment with a catalytic amount of $Cu(OAc)_2$ in *n*-propylamine and purging with O_2 for reoxidation of the Cu^+ formed in the oxidation of the linker group. The copper salt was readily and efficiently separated from the products by treatment of the reaction mixture with 10 equivalents of a copper-chelating polyamine resin (Advanced Chemtech) or by simple filtration through a silica gel column for solid-phase extraction. In both cases examination of the crude reaction products by atomic absorption spectroscopy indicated that more than 99.9 % of the copper had been removed.

A total of 23 differently substituted 2-aminothiazoles were synthesized by using this procedure, and the results are summarized in Table 1. The data demonstrate that the 2-aminothiazoles are obtained in 9-step (*N*-monosubstituted) and 10-step (N,N-disubstituted) sequences in very high overall yield (19–69 %, average yield per step 84–96 %). The synthesis tolerates substantial variation in the structure of the substituents, that is different aromatic, heteroaromatic, and aliphatic groups can be introduced efficiently. The synthesis sequence proceeds so cleanly that the compounds are obtained after cleavage of the traceless linkers in excellent purity (81–99 %) without any further separation and purification steps. In any case they are pure enough to be employed directly for further purposes, for example biological testing. Of particular interest is the mildness of the conditions required for the completely selective cleavage of the traceless hydrazide linker. In the presence of catalytic amounts of the copper salt employed, even oxidation-sensitive functional groups like furans, thiophenes, and sulfides are not attacked at all.

From the different biological and pharmacological activities of compounds with the 2-aminothiazole scaffold we were particularly intrigued by the ability of certain 2-aminothiazole derivatives to inhibit cyclin-dependent kinases (CDKs, see above).[12] These serine/threonine kinases drive and control cell cycle progression and have essential roles in cell proliferation[18a,19a] and at least two CDK inhibitors are undergoing human clinical trials to suppress tumor growth.[18,19] Given the relevance of these proteins we investigated the 2-aminothiazoles as possible inhibitors of CDK-2 and CDK-4. However, none of the compounds showed appreciable inhibitory activity, which indicates that the individual decoration of the 2-aminothiazole core is paramount to achieving biological activity in the compound class.

In the light of the high similarity among the structure of the ATP-binding domains of protein kinases[18,19] and the notion that this evolutionary conservatism of Nature can be employed as the guiding principle for the development of compound libraries,[20] the library was screened for possible

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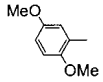
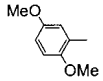
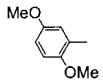
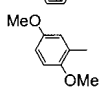
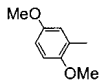
Table 1. Results of the traceless solid-phase synthesis of 2-aminothiazoles **14**.

Entry	R^1	R^2	R^3	R^4	Overall yield [%][a]	Purity [%][a]
14/1		H	H		69	96
14/2		H	H		49	99
14/3		H			34	86
14/4		H			19	99
14/5		H	H		29	89
14/6			H		28	99
14/7					31	92
14/8			H		38	99
14/9			H		25	92
14/10			H		42	99
14/11			H		20	86
14/12					30	87
14/13			H		47	81
14/14			H		35	84
14/15					19	98
14/16			H		24	99
14/17					35	86
14/18			H		20	82
14/19			H		33	85
14/20					35	81
14/21					28	93
14/22			H		42	82
14/23			H		31	84

[a] Yield and purity were determined for the crude products after release from the solid support and SPE without further purification. Purity was determined by means of HPLC and GC-MS. The structures of all compounds were confirmed by NMR.

inhibitors against receptor tyrosine kinases (RTKs), selected to cover a wide spectrum of biological activities. To this end, epidermal growth factor receptor (EGFR; ErbB-1),[21] ErbB-2 (Her-2/Neu), insulin-like growth factor 1 receptor (IGF1R),[22] fibroblast growth factor receptor 1 (FGFR1),[23] vascular endothelial growth factor receptors 2 and 3 (VEGFR-2 and -3), and Tie-2[24–26] were chosen as test systems.

The library of the 2-aminothiazoles did not contain any inhibitor of EGFR, ErbB-2, and IGF1R which warranted further investigation. Remarkably, however, six compounds turned out to be inhibitors of Tie-2 and five compounds inhibited VEGFR-2 from a library of only 23 aminothiazoles (Table 2). In addition, a potent inhibitor of the FGFR-1 and two inhibitors of VEGFR-3 were identified. This means that three of the most important regulators of angiogenesis (the development of new blood vessels from pre-existing ones) and lymphoangiogenesis can be inhibited by the prepared 2-aminothiazoles..

Angiogenesis is central to wound repair, inflammation, and embryonic development. Futhermore, aberrant angiogenesis is considered to be a key step in tumor growth, spread, and metastasis.[24,25] Vascular development depends on the endothelium-specific vascular endothelial growth factor receptors 1–3 (VEGFR1–3) and the Tie-2 receptor.[26] All these receptors have been implicated in tumor angiogenesis,[27–31] and antagonization of Tie-2, VEGFR-2, or VEGF-D (a ligand of VEGFR-3) inhibits tumor growth and tumor metastasis in vivo.[30,32,33] The development of low-molecular-weight inhibitors of these receptor tyrosine kinases is among the most promising approaches for the development of new, alternative antitumor drugs, and several inhibitors of VEGFR-2 are in clinical trials.[34,35] The combination of VEGFR-2 inhibitors with Tie-2 antagonists should potentiate their antiangiogenic effects.[29] Furthermore, inhibitors of VEGFR-3 would suppress the lymphogenic metastasis of tumors. To date however, only a few cases of small-molecule inhibitors of Tie-2 and VEGFR-3 have been reported.[36]

Several of the already known VEGFR-2 and Tie-2 inhibitors display nanomolar affinities towards the isolated kinases and are significantly more potent than the inhibitors identified in this study. However, the 2-aminothiazole inhibitors described above represent a new structural class of VEGFR-2/3 and Tie-2 inhibitors and, in particular, they are clearly differentiated from the other known inhibitors by their dual specificity for VEGFR-2 and Tie-2.

In conclusion we have developed an efficient method for the traceless synthesis of 2-aminothiazoles that display dual specifity against the receptor tyrosine kinases VEGFR-2 and Tie-2. This finding opens possibilities for the suppression of angiogenesis and for the development of new antitumor agents. The synthesis method should rapidly give access to a

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Table 2. Inhibition of different receptor tyrosine kinases by 2-aminothiazoles **14** (IC_{50} [μM]).[a, b].

Entry	Compound	VEGFR-2	VEGFR-3	Tie-2	FGFR 1
1	**14/1**	–	–	21	–
2	**14/2**	–	–	13	–
3	**14/7**	7.4	44	9.8	8.6
4	**14/8**	31	–	4.8	–
5	**14/14**	12	41	–	–
6	**14/20**	86	–	28	–
7	**14/23**	63	–	31	–

[a] None of the introduced compounds inhibited IGF1R, EGFR, or ErbB-2. [b] To assay the inhibitory activity, the kinase-catalyzed phosphorylation of poly(Glu-Tyr) in the presence of varying concentrations of inhibitor was determined. The kinases were employed as fusion proteins of glutathione-S-transferase (GST) and the respective kinase domain. The relative amount of phosphorylated substrate was quantified by means of an anti-phosphotyrosine enzyme-linked immunosorbent assay (ELISA), which employed an anti-phosphotyrosine antibody conjugated to horseradish peroxidase (POD). The bound antibody was detected by the light emission after addition of a chemiluminescence substrate for POD.

much larger library of 2-aminothiazoles from which dual-selective VEGFR-2 and Tie-2 inhibitors with enhanced biological potency may be identified that could be developed into a new class of anti-angiogenesis drugs.

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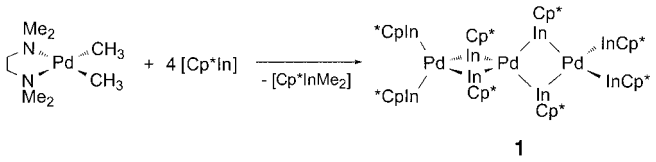
$[Pd_3(InCp^*)_4(\mu_2\text{-}InCp^*)_4]$: Three Linearly Arranged Palladium Atoms Wrapped into a Fluxional Shell of Eight InCp* Ligands**

Tobias Steinke, Christian Gemel, Manuela Winter, and Roland A. Fischer*

In 1999 Murugavel and Chandrasekhar stated in a Highlight article in this journal on monovalent Group 13 organometallic compounds that "the use of these compounds … in transition metal chemistry is likely to have a huge impact on the way new metal–metal bonds are made in the future … and there is no doubt that we will be witnessing the synthesis of a whole range of new cluster types in the future."[1] The monovalent homoleptic complexes $[M\{EC(SiMe_3)\}_4]$ (M = Ni, E = Ga; M = Pt, E = In) synthesized by Uhl et al. in 1998[2] and $[Ni(GaCp^*)_4]$ (Cp^* = pentamethylcyclopentadienide) synthesized by Jutzi et al. in 1999[3] confirmed this statement. Hitherto, most of the studies concerning complexes of these new ligands ER (E = Al, Ga, In, R = Alkyl, Aryl), which are isolobal to CO, were focused on the coordination to transition metal carbonyl fragments $[(CO)_nM_a]$,[4,5] a chemistry that has also been stimulated by our work on $[(CO)_4Fe(AlCp^*)]$.[6] Constitution and structural characteristics of new [GaCp*]-substituted Ni_4 and Rh_6 carbonyl clusters or $[\{(CpNi)(\mu\text{-}AlCp^*)\}_2]$, which were synthesized by Jutzi et al.[7] and Schnöckel et al.,[8] respectively, are directly related to classical transition metal carbonyl cluster structures. Another heuristically valuable analogy of ER ligands to phosphanes is observed for the compounds $[(dcpe)Pt(ER)_2]$ (dcpe = bis(dicyclohexyl)phosphanylethane),[9] a series related to $[Pt(PR_3)_4]$. We recently synthesized the Pt_2Ga_5 complex $[Pt_2(GaCp^*)_2(\mu_2\text{-}GaCp^*)_3]$ selectively by reaction of $[Pt(\eta^2\text{-}C_2H_4)_3]$ and an excess of [GaCp*], and this complex represents the first example of a homoleptic complex of the new series $[M_a(ER)_b]$ $(b > a > 1)$.[10] No structural analogue is known in carbonyl or phosphane cluster chemistry for this complex. Further investigations of this chemistry led us to the title compound $[Pd_3(InCp^*)_4(\mu_2\text{-}InCp^*)_4]$ (**1**).

When $[(tmeda)Pd(CH_3)_2]$ (tmeda = *N*,*N*,*N*′,*N*′-tetramethylethylenediamine) is treated with an excess of [InCp*] in solution in hexane (Scheme 1), and the reaction mixture is warmed to 60 °C, the trinuclear complex $[Pd_3(InCp^*)_4(\mu_2\text{-}InCp^*)_4]$ (**1**) is quantitavely formed, instead of the expected monomeric complex $[Pd(InCp^*)_4]$ (**2**). Complex **1** can be crystallized from benzene as large deep red single crystals in reproducible yields of 90%. The molecular structure of **1** (Figure 1) exhibits three edge-bridging $PdIn_4$



1

Scheme 1. Preparation of **1** from $[Pd(tmeda)(CH_3)_2]$ and [Cp*In].

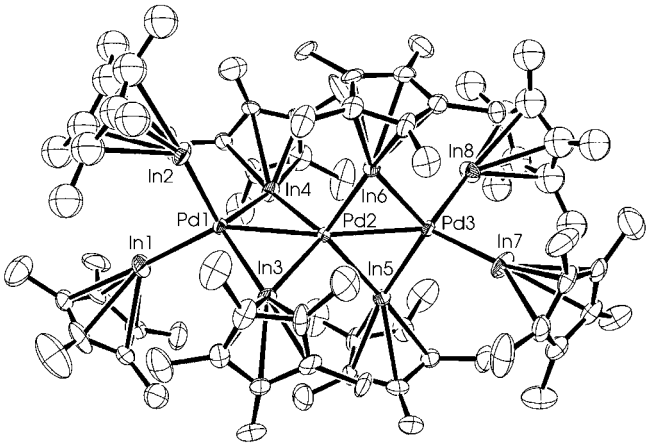


Figure 1. Structure of **1** (ORTEP plot; ellipsoids for 30% probability). Hydrogen atoms are omitted for clarity. Selected distances [Å] and angles [°]: $Cp^*_{centroid}$-In1 2.247, $Cp^*_{centroid}$-In2 2.343, $Cp^*_{centroid}$-In3 2.239, $Cp^*_{centroid}$-In4 2.236, $Cp^*_{centroid}$-In5 2.231, $Cp^*_{centroid}$-In6 2.246, $Cp^*_{centroid}$-In7 2.276, $Cp^*_{centroid}$-In8 2.315, $Cp^*_{centroid}$-In1- Pd1 153.8, $Cp^*_{centroid}$-In2- Pd1 147.3, $Cp^*_{centroid}$-In7-Pd3 174.3, $Cp^*_{centroid}$-In8- Pd3 157.0.

tetrahedrons. The three central palladium atoms are arranged with only a small deviation from linearity of 10° (Figure 2). The distortion of the $PdIn_4$ tetrahedrons is expressed in the In-Pd-In angles, which are smaller than 109° for the terminal In atoms (101.3° and 104.0°) and larger than 109° for the bridging In atoms (114.0° to 116.6°). Correspondingly the dihedral angles In3-Pd1-Pd2-In4 and In6-Pd2-Pd3-In5 deviate from planarity (22.34° and 6.67°). The two bridging In atoms that exihibit the higher deviation (In3, In4) are bent towards the site slightly opened by the Pd-Pd-Pd angle, resulting in a butterfly-shaped structure. The terminal Pd–In distances (2.54–2.57 Å) are somewhat shorter than the bridging ones (2.58–2.61 Å); the Pd–In distances around the central Pd2 atom are the longest (about 2.63 Å). In comparison, the Pd–In distances in the intermetallic phase Pd_3In_7, which contains

[*] Prof. Dr. R. A. Fischer, T. Steinke, Dr. C. Gemel, M. Winter
Lehrstuhl für Anorganische Chemie II - Organometallics & Materials
Ruhr-Universität Bochum
44780 Bochum (Germany)
Fax: (+49) 234-321-4174
E-mail: roland.fischer@ruhr-uni-bochum.de

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