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Regiodivergent Synthesis of 11*H*-Indolo[3,2-*c*]quinolines and Neocryptolepine from a Common Starting Material

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A large number of diversely functionalized analogs of the bioactive natural products neocryptolepine and isocryptolepine have been prepared from a series of 3-bromoquinoline derivatives. The neocryptolepines were obtained by a Pd^0-catalyzed C–C bond coupling followed by C–N bond formation in yields up to 80%, whereas the indoloquinolines were prepared by a Suzuki-Miyaura cross-coupling followed by azidation-photochemical cyclization in yields ranging from traces to 95% yield.

Introduction

Derivatives of indoloquinolines such as isocryptolepine (Figure 1) and neocryptolepine (Figure 2),[1] whose tetracyclic aromatic structural motifs are isomeric, constitute an important class of biologically active compounds that are found in a range of natural products,[2] agrochemicals,[3] and drug candidates.[4] A range of synthetic strategies has been utilized for the formation of the two tetracyclic compounds (Figures 1 and 2).

The compounds exhibit a variety of pharmacological properties,[2,5] and of particular interest is the activity of some derivatives against methicillin-resistant *Staphylococcus aureus* (MRSA), a hard-to-treat bacterial infection with antibiotic resistance, unresponsive to many broad-spectrum β-lactam antibiotics,[6] and drug-resistant biofilms, which are rapidly becoming a global health threat.[7]

With this as a backdrop, we wanted to expand the selection of both 11*H*-Indolo[3,2-*c*]quinolines, isocryptolepines, and neocryptolepines to see if the bioactivity and pharmaceutical potential could be improved by variation of the substituents attached to rings A and D of their aromatic cores (see Figure 1 and 2). In order to make the process as effective as possible, we aimed at constructing both groups of derivatives from a set of common starting materials,[8] and based on our successful synthesis of isocryptolepine from 3-bromoquinoline (**3a**), we decided indeed to opt for this quinoline and derivatives thereof as the starting materials.[9] Thus, we started searching for reaction conditions which would make the synthesis of both targets possible from 3-bromoquinoline derivatives.

Results and Discussion

First, the reaction sequence applied to prepare isocryptolepine was attempted to make isocryptolepine derivatives, but to our disappointment, the microwave-induced C–H activation/C–N bond-formation step involved[9b] showed no tolerance for functionalized 3-bromoquinolines. Without exception the crude reaction mixtures contained numerous products (up to 12

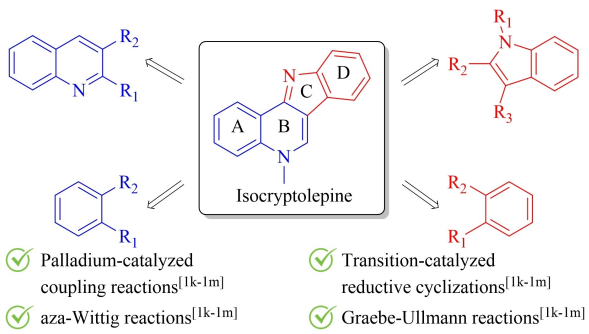

Figure 1. Common strategies for the formation of isocryptolepine.

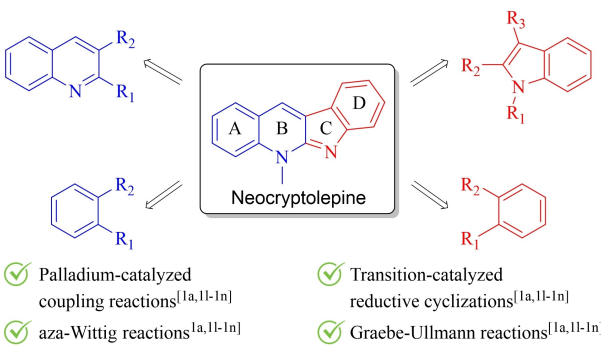

Figure 2. The most utilized strategies for the synthesis of neocryptolepine.

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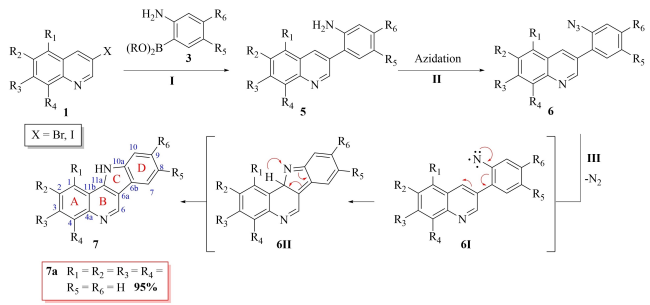
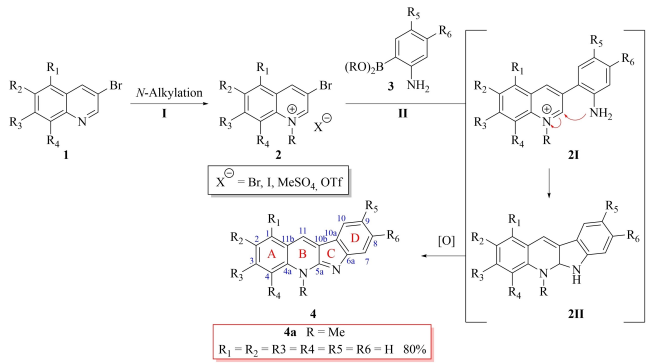
according to TLC analysis) that furnished intractable NMR spectra. We have also reported the synthesis of isocryptolepine via a Suzuki-Miyaura cross-coupling-azidation-thermally induced nitrene insertion sequence,[9c] but a major drawback of this approach is the harsh reaction conditions (180 °C) of the nitrene-insertion step. An alternative way of generating aryl nitrenes was therefore tried, *viz.* through photolysis of the corresponding aryl azides, which is often facile even at room temperature.[10] The reaction appeared to be solvent dependent, but after extensive screening, α,α,α-trifluorotoluene (TFT) appeared to stand out and afforded isocryptolepine precursors **7** in better than 90% yield in the best cases (Scheme 1). As indicated, the photochemical transformation presumably proceeds through a reactive singlet nitrene, which undergoes cyclization followed by a 1,5-hydrogen shift.

After extensively exploring various reaction conditions, we found that by exposing compound **2a** (R = Me, $R_1 = R_2 = R_3 = R_4 = H$) to a Suzuki-Miyaura cross-coupling reaction, the target neocryptolepine (**4a**) could be produced in just two steps from the corresponding 3-bromoquinoline (Scheme 2). Indeed, the bromoquinolinium ion **2a** was simply obtained by an *N*-alkylation procedure using standard reagents and conditions without the need for purification by silica gel column chromatography. Then, carrying out a standard Suzuki-Miyaura cross-coupling protocol between the bromoquinolinium ion **2a** and boronic acid **3a** ($R_5 = R_6 = H$), yielded intermediate **2I**, which was sufficiently electrophilic for the amino group to directly facilitate ring closure via a nucleophilic substitution of hydrogen[11] and construct neocryptolepine (**4a**) in excellent yield (80%) (Scheme 2).



Scheme 1. Synthetic approach to the formation of isocryptolepine precursors - 11*H*-indolo[3,2-*c*]quinolines **7**. Conditions: I: 3 (1.2-1.3 equiv.), $Pd(PPh_3)_4$ (5 mol%), Cs_2CO_3 (3.2-3.3 equiv.), DME:H_2O (5:1), 80 °C; II: 1) HCl (37%), $NaNO_2$ (0.4 M), 0 °C, 1.5 h; 2) NaN_3, NaOAc, 0 °C, 1 h; III: hν, $PhCF_3$, rt.



Scheme 2. Synthetic approach to the formation of neocryptolepines **4**. Conditions: I: RX, solvent; II: 3 (1.2–1.3 equiv.), $Pd(PPh_3)_4$ (5 mol%), Cs_2CO_3 (3.3–4.2 equiv.), DME/H_2O (5:1), 80 °C.

After having established a synthesis for both indoloquinolines **7** and neocryptolepines **4** from a set of common starting materials, it was time to evaluate the scope and limitation of the novel synthetic strategies.

In order to investigate the scope and limitations of the novel photolytic conversion of aryl azides **6** to indoloquinolines **7**, it was first necessary to prepare a large assortment of diversely functionalized biaryls **5** to facilitate the proceeding transformations. This was carried out by subjecting commercially available reagents to our optimized Suzuki-Miyaura cross-coupling protocol to give biaryls,[5,9] transformation of the amino group to an azido moiety under standard conditions to give aryl azides **6**. Finally, photolytic decomposition of the azido group granted access to 19 diversely substituted indoloquinolines **7** in up to 95% yield (Scheme 3). Contrary to our novel neocryptolepine **4** syntheses, no clear trends with regards to the electronic nature of the substituents emerged from this study, however, the methodology appeared to be less robust, and the observed yields were inconsistent. The photolytic step moreover showed zero tolerance to nitro substitutions, with the puzzling exception of the formation of compound **7g** in 77% yield (Scheme 3). Nitro aromatics are known to act as chromophores in photochemical transformations and can give rise to a large series of reduction products, such as anilines, hydroxylamines, azo compounds and nitroso compounds.[12] It thus seems plausible that our evaluated nitro-functionalized aryl azides underwent a multitude of unwanted photocatalyzed transformations, leading to poor conversion into the desired indoloquinolines, however, none of the aforementioned reduction products were ever observed. Quantum chemical investigations into the successful formation of nitro-functionalized compound **7g** is currently underway in order to explain the divergent behavior compared to the other evaluated nitro compounds. In addition to poor tolerance to nitro-functionalizations, the method was also sensitive towards ketones. Ketones are also regarded as a somewhat photolabile group and may be transformed into ketyl radicals, eventually producing secondary alcohols.[13] This would likely account for the poor conversion into the desired ketone-containing indoloquinolines **7** (Scheme 3, compounds **7d**, **7e**, and **7s**). Intriguingly, the photocyclization to give cyano-substituted indoloquinoline **7i** (31%) also yielded small quantities of its regioisomeric product, namely **7ia** (5%), an indolo[2,3-*b*]quinoline. This presents the only case in which the formation of two regioisomers were observed, the exact reason for why is uncertain. The major limitation in the photolytic cyclization, however, appeared to be related to the solubility of the target indoloquinolines **7** in TFT. During the photolysis, several of the reaction mixtures began producing a precipitate, presumably the desorbed indoloquinolines, coating the glassware and obstructing the light from the lamp.

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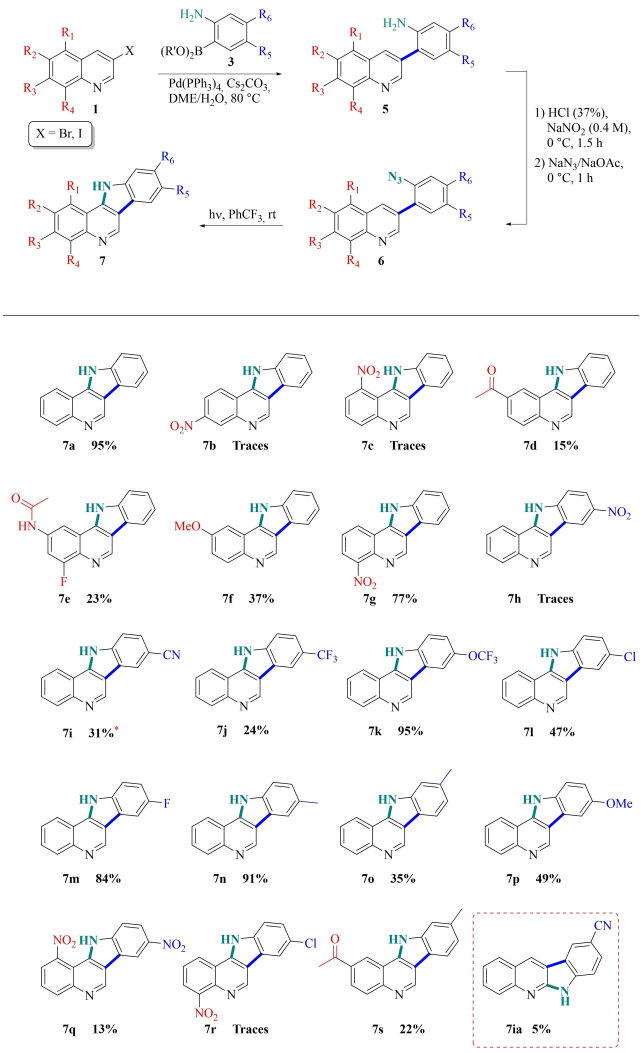
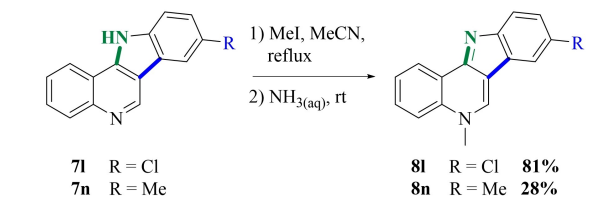


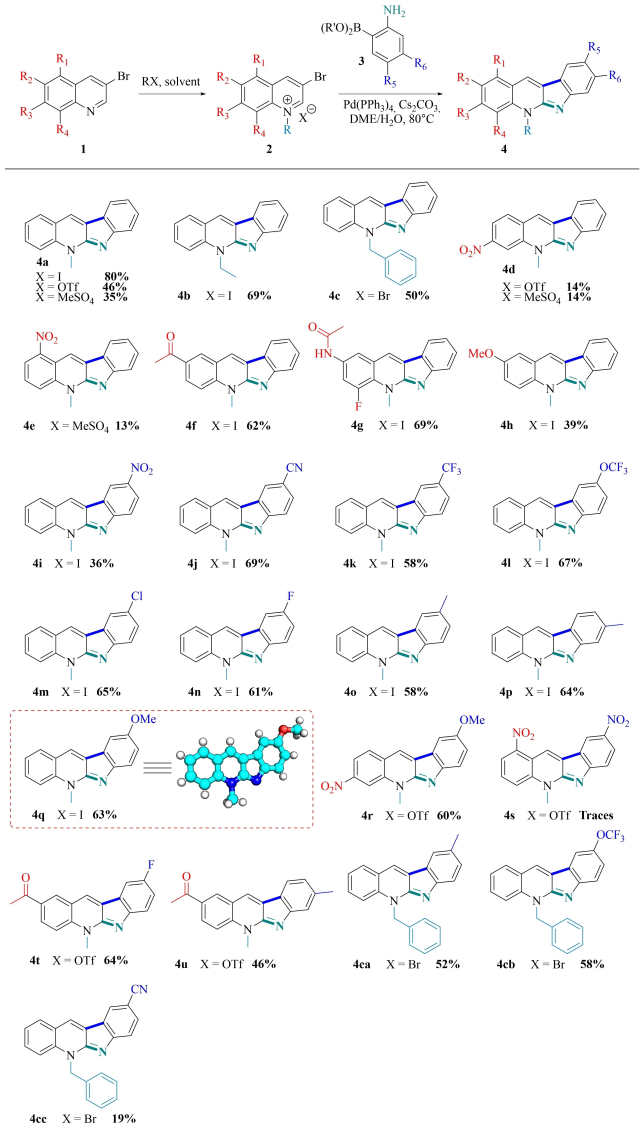
Scheme 3. Scope of Pd-catalyzed C–C coupling, azidation and photochemical cyclization to give 11*H*-indolo[3,2-*c*]quinolines **7**.

Finally, the applicability of our photolytic approach was demonstrated by transforming two of the prepared indoloquinolines **7** to the corresponding natural product derivatives. Isocryptolepine derivatives **8** was synthesized by a standard *N*-methylation approach using a large excess of methyl iodide in refluxing acetonitrile to give the desired compounds in acceptable to excellent yields (Scheme 4).[9]

To ascertain the functional group tolerance of the novel cascade neocryptolepine approach, a wide array of functionalized bromoquinolinium salts **2**[14] and boronic acid esters **3**[15] were purchased or prepared following various literature procedures (see experimental for details). Then, the cascade Suzuki-Miyaura cross-coupling-intramolecular cyclizations were carried out with the optimized reaction protocol to grant access to 24 diversely functionalized neocryptolepines **4** in up to 80% yield (Scheme 5). The method showed a broad tolerance to most substitution patterns, however, slightly favoring the presence of electron-withdrawing substituents on the quinoline moiety. This is likely the result of an increase in the electrophilic character of the quinoline core of intermediate **2l** towards the amino group during cyclization (Scheme 2). Similarly, the replacement of the *N*-methyl group for an *N*-ethyl or *N*-benzyl group was unfavorable in terms of yield (Scheme 5, compounds **4ca**–**4cc**). While the reaction protocol showed an overall high robustness to most functionalizations, it displayed a poor tolerance toward most nitro-functionalization (Scheme 5, com-



Scheme 4. Synthesis of isocryptolepine derivatives **8** by *N*-alkylation.



Scheme 5. Scope of Pd-catalyzed cascade C–C coupling and C–N bond formation to give functionalized neocryptolepines **4**.

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pounds **4d**, **4e**, **4i**, and **4s**). It was, however, possible to counter this by placing a strongly electron-donating group *para* to the amino group, which resulted in a yield of 60% for nitro-functionalized compound **4r**. An X-ray diffraction structure was obtained for compound **4q** to confirm the structure since our NMR data for that compound did not fully match the data reported in the literature[3a] due to the use of a different solvent during NMR analysis.

Conclusion

We have identified 3-bromoquinoline as a regiodivergent intermediate which when subjected to two different sets of novel reaction conditions will grant access to both the natural product neocryptolepine (**4a**) and the isocryptolepine precursor **7** in excellent yields. The scope and limitations of the novel reaction protocols was evaluated by preparing 24 diversely functionalized neocryptolepines **4** in up to 80% yield, where the methodology showed a greater robustness towards EWGs on the quinoline core. The novel photochemical pathway was evaluated by preparing 19 diversely functionalized indoloquinolines **7** in up to 95% yield. The investigation confirmed that the presence of photolabile groups, such as nitro groups and ketones, was poorly tolerated, which is in accordance with previous studies. Moreover, the photochemical reaction was revealed to be highly solvent sensitive, revealing the need for further solvent screenings in order to optimize the reaction yields. Finally, we synthesized two isocryptolepine derivatives **8** to show the applicability of our photochemical approach. Results from the ongoing biological evaluation of these compounds will be reported in due course.

Experimental Section

Synthesis of 2-aminophenylboronic acid pinacol esters: 2-Aminophenylboronic acid pinacol esters employed in this work was synthesized in a single step by palladium-catalyzed borylation of the corresponding substituted 2-haloanilines following the procedure reported by Zhou and Driver.[2]

General Procedure: To a mixture of 2-haloaniline (1 equiv.), anhydrous Et_3N (4 equiv.), Pd^{II} (10 mol%) in an appropriate amount of anhydrous dioxane under an argon atmosphere, was added 4,4,5,5-tetramethyl-1,3,2-dioxaborolane (3 equiv.) dropwise. The resulting mixture was refluxed until completion as indicated by TLC analysis. The crude mixture was then allowed to cool to rt and quenched by addition of suitable amounts of sat. aq. NH_4Cl and subsequently extracted with CH_2Cl_2 (3×10 mL). The combined organic phases were washed (1×10 mL H_2O, 1×10 mL brine), dried ($MgSO_4$), filtered and concentrated in vacuo. The concentrate was then evaporated onto celite and purified by column chromatography using the eluents reported below in order to give target compounds **3**.

General procedure synthesis of bromoquinolinium ions 2 To a solution of 3-bromoquinoline (**1a**) in an appropriate amount of solvent, the alkylation reagent (2.5–10 equiv.) was added, and the resulting mixture was stirred at the required temperature under an argon atmosphere until completion as indicated by TLC analysis. The formed precipitate was thoroughly washed with either n-hexanes or $CHCl_3$, filtered and dried under reduced pressure to give the target quinolinium salts **2**, which were used directly without further purification. In the reactions employing dimethyl sulfate as an alkylation reagent, the crude was also washed with water.

General procedure for the synthesis of neocryptolepines 4 by cascade C–C and C–N coupling reaction To a solution of quinolinium salt **2** (1 equiv.) in an appropriate amount of 1,2-dimethoxyethane (DME) under an argon atmosphere was added boronic acid 3 (1.2–1.3 equiv.), an aqueous solution of Cs_2CO_3 (3.2–4.2 equiv.) and $Pd(PPh_3)_4$ (5 mol%). The resulting reaction mixture was stirred at 80 °C until completion as indicated by TLC analysis. The crude mixture was then allowed to cool to rt and the volatiles were removed under reduced pressure. The concentrate was evaporated onto celite and purified by column chromatography using the eluents as reported in order to give target compounds **4**.

General procedure for the synthesis of biaryls 5 by Suzuki-Miyaura cross-coupling reaction To a solution of haloquinoline **1** (1 equiv.) in an appropriate amount of DME under an argon atmosphere was added boronic acid or boronic ester **3** (1.2–1.3 equiv.), an aqueous solution of Cs_2CO_3 (3.2–3.3 equiv.) and $Pd(PPh_3)_4$ (5 mol%). The resulting reaction mixture was stirred at 80 °C until completion as indicated by TLC analysis. The crude mixture was then allowed to cool to rt and the volatiles were removed under reduced pressure. The concentrate was evaporated onto celite and purified by column chromatography using the eluents as reported in order to give target compounds **5**.

General procedure for the synthesis of aryl azides 6 by diazotization-azidation Biaryl **5** (1 equiv.) was dissolved in an appropriate amount of aq. HCl (37%) and the mixture was cooled to 0 °C using an ice bath. Then, ice-cooled aq. $NaNO_2$ (0.4 M) was added to the solution dropwise and the resulting mixture was stirred at 0 °C for 1.5 h. An ice-cooled aq. solution of NaN_3/NaOAc (2.1 equiv./14 equiv. in an appropriate amount of H_2O) was added dropwise and the mixture stirred for 1 h while keeping the temperature at 0 °C. The reaction mixture was quenched by addition of suitable amounts of sat. aq. Na_2CO_3 and subsequently extracted with CH_2Cl_2 (3×20 mL). The combined organic phases were washed with water (1×20 mL), brine (1×20 mL), dried ($MgSO_4$), filtered and concentrated in vacuo to give the target compounds **6**.

General procedure for photocyclizations to form indoloquinolines 7 Aryl azide **6** (1 equiv.) in 150 mL α,α,α-trifluorotoluene was bubbled with a steady flow of argon as the mixture was irradiated at ambient temperature until completion as indicated by TLC analysis. The volatiles were then removed under reduced pressure and the concentrate was evaporated onto celite. Finally, the crude mixture was purified by silica gel column chromatography with the eluent as indicated to give target compounds **7**.

General procedure for syntheses to form functionalized isocryptolepines 8 To a solution of indoloquinoline **7** (1 equiv.) in an appropriate amount of acetonitrile, iodomethane (100 equiv.) was added and the resulting mixture stirred at reflux under an argon atmosphere until completion as indicated by TLC analysis. After allowing the reaction mixture to cool to rt, the volatiles were removed under reduced pressure and the concentrate was evaporated onto celite. Purification by column chromatography using the eluent as indicated gave the hydroiodide salt of indoloquinoline **8**. To obtain the free base, the hydroiodide salt was dissolved in a 1:1 mixture of CH_2Cl_2 and NH_3 (aq) (25%) and stirred at rt for 30–45 min. The organic layer was separated, and the aqueous layers were extracted with CH_2Cl_2 (x3) and the combined organic layers were washed with water (x1), brine (x1), dried ($MgSO_4$), filtered and concentrated in vacuo to give the target compound **8**.

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Conflict of Interest

The authors declare no conflict of interest.

Data Availability Statement

The data that support the findings of this study are available in the supplementary material of this article.

Keywords: neocryptolepine · isocryptolepine · palladium catalysis · photochemistry · natural product analogues

[1] For some recent papers describing the synthesis of isocryptolepine and neocryptolepine, see for example: a) C. Thongsornkleeb, J. Tummatorn, S. Ruchirawat, *Chem. Asian J.* **2022**, *17*, e202200040; b) E. N. Thobokholt, E. L. Larghi, A. B. J. Bracca, T. S. Kaufman, *RSC Adv.* **2020**, *10*, 18978–19002; c) E. Schendera, L.-N. Unkel, P. P. H. Quyen, G. Salkewitz, F. Hoffmann, A. Villinger, M. Brasholz, *Chem. Eur. J.* **2020**, *26*, 269–274; d) S. K. Das, S. Roy, H. Khatua, B. Chattopadhyay, *J. Am. Chem. Soc.* **2018**, *140*, 8429–8433; e) A. V. Aksenov, G. D. Aksenov, G. D. Griaznov, N. A. Aksenov, L. G. Voskressensky, M. Rubin, *Org. Biomol. Chem.* **2018**, *16*, 4325–4332; f) T.-Y. Zhang, C. Liu, C. Chen, J.-X. Liu, H.-Y. Xiang, W. Jiang, T.-M. Ding, S.-Y. Zhang, *Org. Lett.* **2018**, *20*, 220–223; g) A. V. Aksenov, D. A. Aksenov, N. A. Orazova, N. A. Aksenov, G. D. Griaznov, A. De Carvalho, R. Kiss, V. Mathieu, A. Kornienko, M. Rubin, *J. Org. Chem.* **2017**, *82*, 3011–3018; h) P. S. Mahajan, V. T. Humne, S. D. Tanpure, S. B. Mhaske, *Org. Lett.* **2016**, *18*, 3450–3453; i) P. S. Volvoikar, S. G. Tilve, *Org. Lett.* **2016**, *18*, 892–895; j) Z.-W. Hou, Z.-Y. Mao, H.-B. Zhao, Y. Y. Melcamu, X. Lu, J. Song, H.-C. Hu, *Angew. Chem. Int. Ed.* **2016**, *55*, 9168–9172; *Angew. Chem.* **2016**, *128*, 9314–9318; k) P. T. Parvatkar, P. S. Parameswaran, *Curr. Org. Synth.* **2016**, *13*, 58–72; l) A. B. J. Bracca, D. A. Heredia, E. L. Larghi, T. S. Kaufman, *Eur. J. Org. Chem.* **2014**, 7979–8003; m) P. T. Parvatkar, P. S. Parameswaran, S. G. Tilve, *Curr. Org. Chem.* **2011**, *15*, 1036–1057; n) O. M. Nadein, D. A. Aksenov, G. M. Aksenov, L. G. Voskressensky, A. V. Aksenov, *Chem. Heterocycl. Compd.* **2019**, *55*, 905–932.

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