HETEROCYCLES, Vol. 106, No. 9, 2023, pp. 1580 - 1588. © 2023 The Japan Institute of Heterocyclic Chemistry
Received, 3rd August, 2023, Accepted, 16th August, 2023, Published online, 17th August, 2023
DOI: 10.3987/COM-23-14893

FACILE PREPARATION OF THE NOOTROPIC AGENT IDRA-21 AND RELATED HETEROCYCLES VIA A ONE-POT IRON-MEDIATED REDOX ANNULATION

Kyosuke Kaneda,[1,2]* Hirotoshi Kabasawa,[1] Syun Nabeki,[1] Uki Matsui,[1] Hiroki Sugiyama,[1] and Takehiro Yamagishi[1,2]

[1]Department of Medicinal Chemistry, Faculty of Pharmaceutical Sciences, Hokkaido University of Science, 7-15-4-1, Maeda Teine Sapporo Hokkaido 006-8585, Japan.
[2]Creation Research of Life Science in KITA-no-DAICHI, Hokkaido University of Science, 7-15-4-1, Maeda Teine Sapporo Hokkaido 006-8585, Japan.
E-mail: kaneda@hus.ac.jp

Abstract – The taking advantage of the redox ability of iron powder allowed us to develop an economical and concise method for the preparation of the 3,4-dihydrobenzothiadiazine 1,1-dioxide (DBTD) and the structurally related heterocycles such as 1,2-dihydroquinazolin-4-one and 1,2,3,4-tetrahydroquinazoline. As an application example, a nootropic agent IDRA-21 was synthesized via one-pot cascade sequences from commercial sources under ambient conditions.

The nootropic agent IDRA-21 (**1**), otherwise known as 7-chloro-3-methyl-3,4-dihydro-2*H*-1,2,4-benzothiadiazine 1,1-dioxide, is a positive allosteric modulator (PAM) of the DL-α-amino-3-hydroxy-5-methylisoxazolepropionic acid receptor (AMPAR), which is a promising target for the treatment of cognitive disorders such as Alzheimer's disease (**Figure 1**).[1]

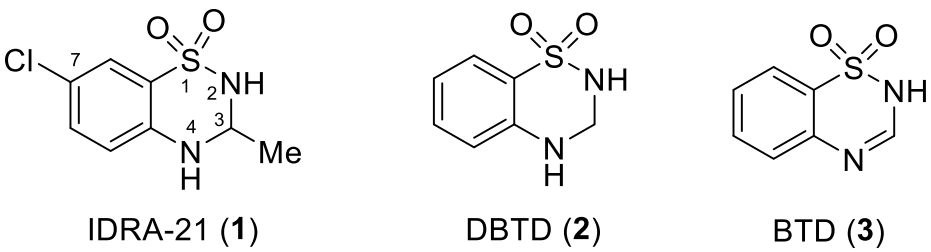
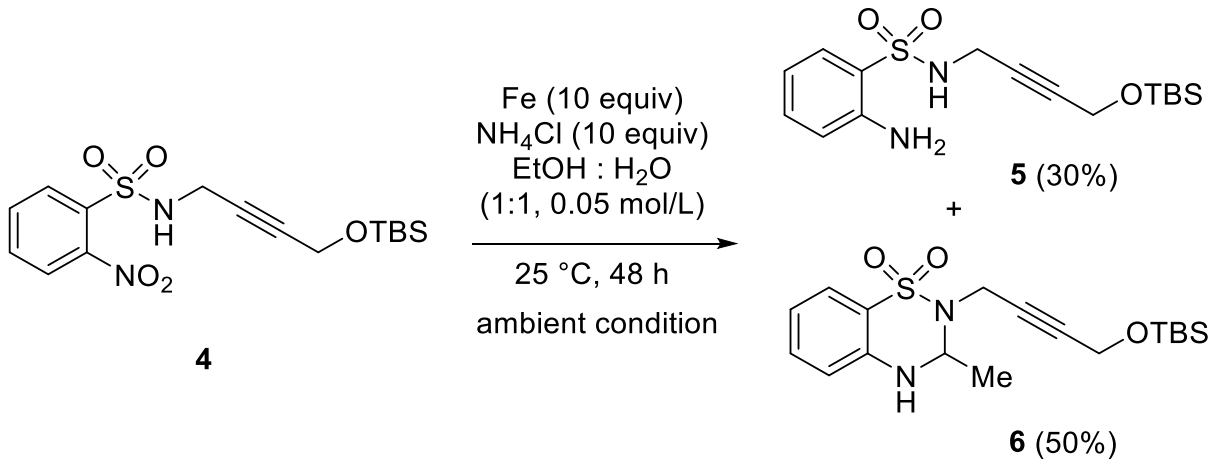


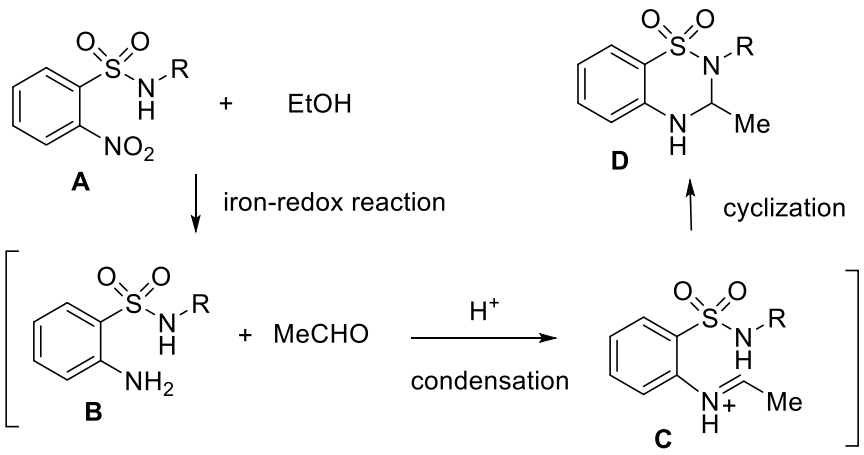
Figure 1. Structures of IDRA-21 (**1**), DBTD (**2**), and BTD (**3**)

To the best of our knowledge, **1** was created by Topliss and co-workers in 1963 as a non-diuretic 3,4-dihydrobenzothiadiazine 1,1-dioxide (DBTD, **2**) and benzothiadiazine 1,1-dioxide (BTD, **3**) derivative during their research into antihypertensive agents.[2] Since then, due to its attractive bioactivity, and in particular its cognitive enhancing activity, **1** has been examined as a structurally important lead compound for the optimization of pharmaceutical profiles.[3] As such, a number of routes to **1** and other DBTD heterocycles have been developed to give efficient, green, simple, and economical methodologies.[3,4] During the nitroarene reduction of **4**,[5] aminoarene compound **5** and DBTD derivative **6** were obtained using the Fe/NH_4Cl/EtOH/H_2O protocol (**Scheme 1**).[6]



Scheme 1. Discovery of a new synthetic route for DBTD derivatives

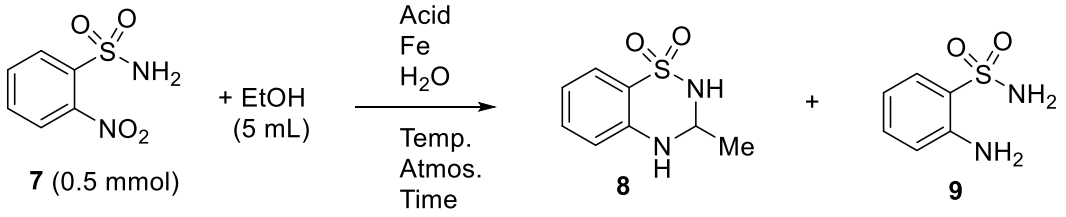
This transformation was of particular interest as it is a facile method for construction of the DBTD core. Although numerous methods have been developed for the synthesis of DBTD and BTD heterocyclic compounds,[4,7] the use of nearly neutral and ambient reaction conditions has not previously been reported. We therefore predicted that the transformation of **A** to **D** (**Scheme 2**) could begin with the iron-powder mediated nitroarene reduction of **A** and the simultaneous in situ generation of acetaldehyde from ethanol.



Scheme 2. Prediction of the reaction mechanism

This could be followed by the dehydrative condensation of 2-aminobenzenesulfonamide **B** with acetaldehyde to produce the cyclic DBTD compound **D** through iminium intermediate **C**. The previously reported metal (iron or tin)-redox one-pot reaction supports this prediction.[8] The aim of this study is therefore to develop a novel economical method for the preparation of DBTD compounds by taking advantage of the redox ability of iron powder.

Table 1. Optimization of the reaction conditions

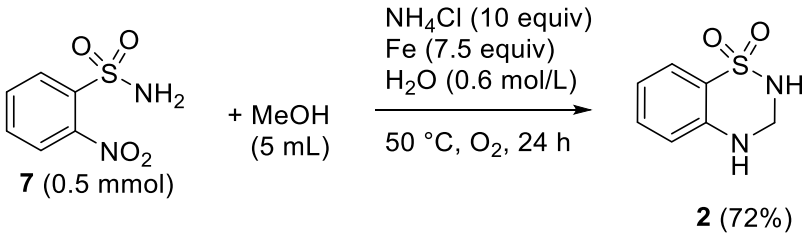


7 (0.5 mmol) **8** **9**

No.	Acid (10 equiv.)	Fe (equiv.)	H_2O (mol/L)	Temp. (°C)	Atmos.	Time (h)	Yield of **8** (%)	Yield of **9** (%)
1	NH_4Cl	10	0.1	25	air	24	27	71
2	NH_4Cl	10	0.1	25	air	96	90	trace
3	NH_4Cl	10	0.1	50	air	24	84	13
4	NH_4Cl	10	0.1	25	O_2	24	63	32
5	NH_4Cl	10	0.1	25	argon	24	4	94
6	HCl	10	0.1	25	air	24	40	55
7	AcOH	10	0.1	25	air	24	97	trace
8	AcOH	10	0.6	25	air	24	95	trace
9	AcOH	7.5	0.6	25	air	24	96	trace

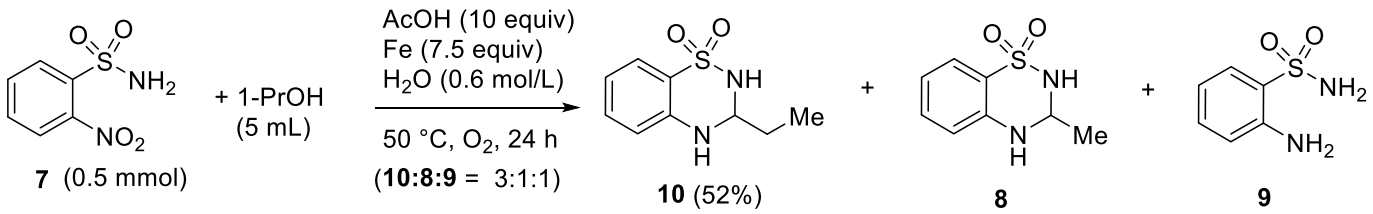
Initially, optimization of the reaction conditions for the transformation of 2-nitrobenzenesulfonamide (**7**) to 3-methyl-3,4-dihydro-2*H*-benzo[*e*][1,2,4]thiadiazine 1,1-dioxide (**8**) was attempted as outlined in **Table 1**. We first attempted the reaction detailed in entry 1, and this gave a 27% yield of the desired cycle **8** and 71% 2-aminobenzenesulfonamide (**9**). The ratio of **8**:**9** was approximately 1:2.6, as calculated by ^{1}H NMR measurements (entry1). Extending the reaction time to 96 h (entry 2) increased the yield of **8** to 90%, with only trace amounts of **9** being obtained. Upon comparison with entry 1, heating to 50 °C (entry 3) increased the yield of **8**, while the use of an O_2 atmosphere (entry 4) also led to an improvement in yield compared to entry 1. In contrast, argon gas inhibited the reaction (entry 5). Therefore, we assumed that oxygen would work as an oxidizing reagent for ethanol to acetaldehyde in situ. On the other hands, replacing NH_4Cl with HCl had a detrimental effect (entry 6), giving a 40% yield of **8** along with 55% **9**. Among the various acids examined, acetic acid (AcOH) appeared to promote the cyclization reaction, giving a 97% yield of **8** as the main product (entry 7). In addition, the concentration of H_2O as a solvent was reduced to 0.6 mol/L (entry

8), while the Fe loading could be reduced to 7.5 equiv. (entry 9). These results indicate that suitable acidity and the presence of oxygen are required to promote the desired transformation.



Scheme 3. Synthesis of DBTD **2** using MeOH

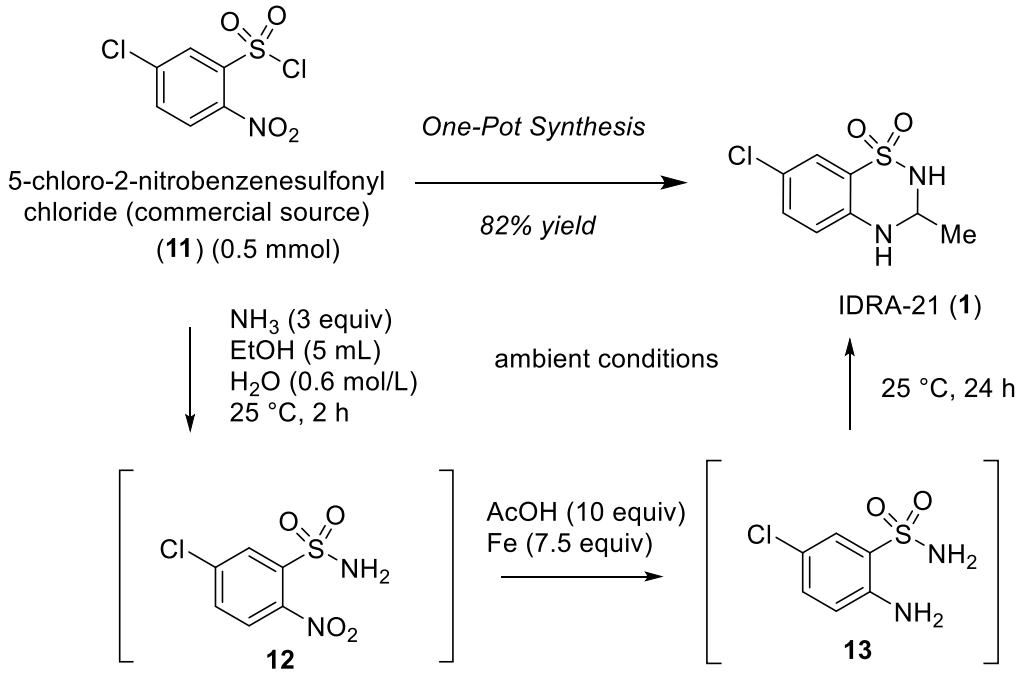
As outlined in **Scheme 3**, the replacement of ethanol with methanol (in the presence of NH_4Cl as the acid) gave a 72% yield of the corresponding DBTD (**2**). In this case, the application of ambient reaction conditions (i.e., room temperature, under air, open reaction flask) reduced the yield of the cyclic product (~50%), likely due to the volatility of the formaldehyde generated in situ. However, equipping the reaction vessel with a sealed O_2 balloon increased the yield once again (72%).



Scheme 4. Use of 1-PrOH as the alcohol

In addition, when AcOH was employed as the acid, the use of 1-propanol instead of ethanol gave a 52% yield of the 3-ethyl DBTD (**10**) along with the 3-methyl DBTD (**8**) and the corresponding amine product (**9**) (3:1:1 ratio, **Scheme 4**). The formation of **8** indicated that AcOH could be inserted into the cyclization product; however, the use of HCl instead of AcOH also gave this product, thereby suggesting that these acids promote a carbon-carbon bond cleavage reaction. The use of NH_4Cl instead of AcOH gave only **9**. The detailed mechanism of this process is currently under investigation in our group.

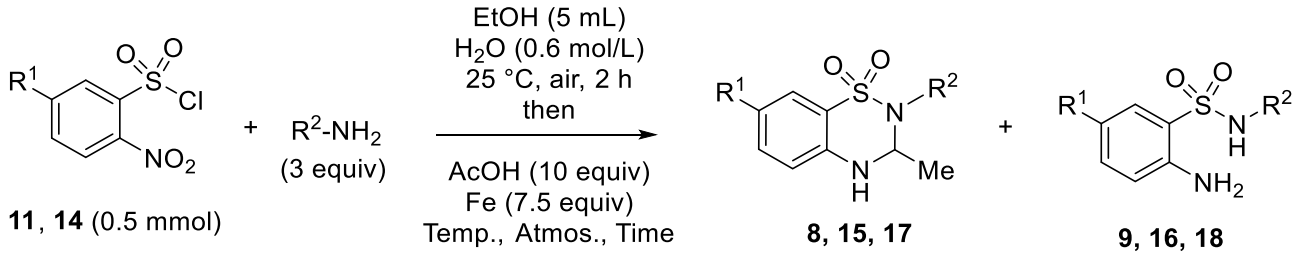
We subsequently applied the optimized reaction conditions to the synthesis of IDRA-21 (**1**). Thus, 5-chloro-2-nitrobenzenesulfonyl chloride (**11**), which is a requisite starting material for the preparation of **1**, was obtained commercially from the Fluorochem Company (UK). Thus, **11** could be converted into 5-chloro-2-nitrobenzenesulfonamide (**12**) in good yield by using aqueous ammonia under ambient condition. Although we initially attempted isolation of the intermediate **12**, we found that this isolation step could be omitted, and we explored one-pot procedure.



Scheme 5. The one-pot synthetic route to IDRA-21(**1**)

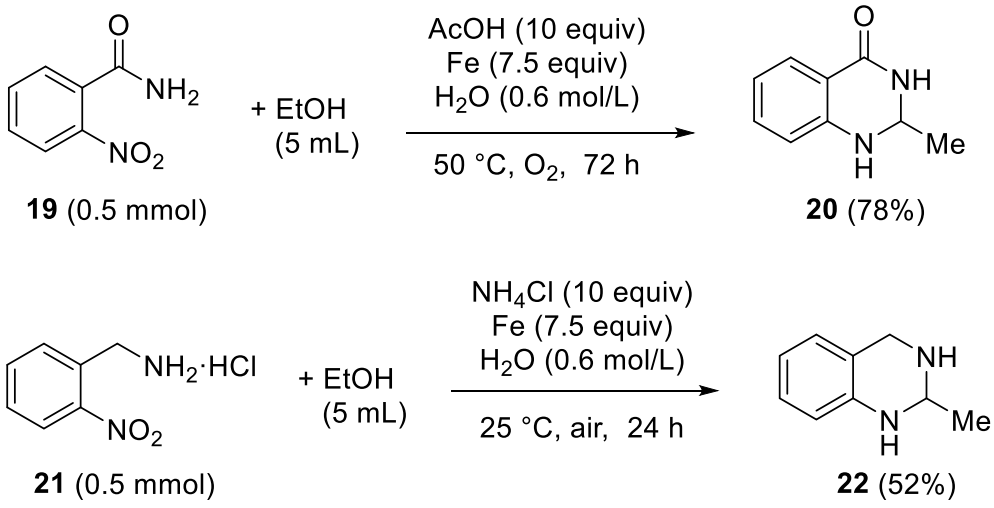
Consequently, the one-pot synthesis of **1** starting from **11** (via **12** and **13**) was achieved in 82% yield via a sulfonamidation/redox-reaction/cyclization sequence under ambient conditions, as depicted in **Scheme 5**. The operational procedure is particularly facile, through the simple addition of NH_3, EtOH, H_2O, Fe, and AcOH at 25 °C. In addition, we note that although this system employs 3 equiv. of NH_3 as the nitrogen source, the in situ generated NH_4Cl did not affect the remainder of the reaction sequence. Furthermore, **1** was obtained in sufficient purity upon filtration and extraction with ethyl acetate. To the best of our knowledge, this route is the most simple and economical preparation of IDRA-21(**1**) reported to date.

Table 2. Synthesis of DBTD derivatives via the one-pot protocol



No.	Substrate		Amine	Temp. (°C)	Atmos.	Time (h)	DBTD derivative		Aminoarene	
		R^1	R^2					Yield (%)		Yield (%)
1	**14**	-H	-H	25	air	24	**8**	89	**9**	trace
2	**14**	-H	-Me	50	O_2	24	**15**	56	**16**	12
3	**11**	-Cl	$-CH_2CH{=}CH_2$	60	O_2	48	**17**	43	**18**	35

We subsequently applied the one-pot system starting from sulfonyl chlorides **11** and **14** in the preparation of 2-substituted DBTD derivatives, and the results are outlined in **Table 2**. As shown in entry 1, the combination of 2-nitrobenzenesulfonyl chloride (**14**) with ammonia gave the desired DBTD derivative **8** in 89% yield. The replacement of ammonia with methylamine (entry 2) then gave the corresponding 2-methyl DBTD **15** in 56% yield, along with aminoarene **16** as a side product. Due to steric hindrance of the methylamine (R^2 = Me), carrying out the same reaction at 25 °C under air gave only a trace amount of **15**. Although further optimization is necessary, the combination of 5-chloro-2-nitobenzenesulfonyl chloride (**11**) and allylamine (entry 3) gave 2-allyl DBTD **17** in a 43% yield along with aminoarene **18** in 35% yield. These results indicate that our developed method is suitable for the preparation of 2-substituted DBTD (N-R^2) derivatives using different amines; however, we note that harsher reaction conditions were required to reach satisfactory yields.



Scheme 6. Syntheses of other *N*-containing heterocycles

To further expand the substrate scope and establish the generality of this protocol, it was applied in the syntheses of dihydroquinazolinone and tetrahydroquinazoline heterocycles. These heterocycles are important scaffolds in numerous bioactive natural products and pharmaceuticals.[9] As shown in **Scheme 6**, 2-nitrobenzamide (**19**) was successfully converted into the corresponding 2-methyl-2,3-dihydroquinazolin-4(1*H*)-one (**20**) in 78% yield in the presence of 10 equiv. AcOH and 7.5 equiv. Fe in H_2O at 50 °C under an O_2 atmosphere for 72 h. Upon carrying out this reaction at 25 °C under an air atmosphere for 24 h, 2-aminobenzamide was obtained as a major product. Furthermore, 2-nitrobenzylamine hydrochloride (**21**) was converted into 2-methyl-1,2,3,4-tetrahydroquinazoline (**22**) in 52% yield in the presence of 10 equiv. NH_4Cl and 7.5 equiv. Fe in H_2O at 25 °C under air

for 24 h. In the presence of AcOH, **22** was isolated in a low yield due to the formation of numerous side products.

In summary, we herein developed and optimized a one-pot cascade process mediated by the redox ability of iron for the effective synthesis of the nootropic agent IDRA-21 and related compounds, such as dihydrobenzodithiadiazine 1,1-dioxide (DBTD) derivatives and *N*-heterocycles. Our method allowed the use of general chemicals such as NH_3, Fe, EtOH, H_2O, and AcOH under ambient conditions, and the overall procedure could be carried out easily in the laboratory. We therefore believe that our report will contribute to the further enhancement of economical routes to nootropic agents and the generation of novel related pharmaceuticals.

EXPERIMENTAL

The procedure of some experimental details and characterization of newly synthesized compounds are in the supporting information.

SUPPORTING INFORMATION

Supplementary (IR, ^1H and ^{13}C NMR, MS spectra, etc.) data associated with this article can be found, in the online version, at URL: https://www.heterocycles.jp/newlibrary/downloads/PDFsi/28012/106/9.

CONFLICT ON INTEREST

The authors declare no conflict of interest, financial or otherwise.

ACKNOWLEDGEMENTS

Financial assistance from the Hokkaido University of Science is gratefully acknowledged.

REFERENCES

1. (a) F. Impagnatiello, A. Oberto, P. Longone, E. Costa, and A. Guidotti, *Proc. Natl. Acad. Sci. USA*, 1997, **94**, 7053; (b) A. Arai, A. Guidotti, E. Costa, and G. Lynch, *Neuroreport*, 1996, **7**, 2211; (c) D. M. Thompson, A. Guidorri, M. Dibella, and E. Costa, *Proc. Natl. Acad. Sci. USA*, 1995, **92**, 7667; (d) I. Zivkovic, D. M. Thompson, M. Bertolino, D. Uzunov, M. DiBella, E. Costa, and A. Guidotti, *J. Pharmacol. Exp. Ther.*, 1995, **272**, 300.
2. J. G. Topliss, M. H. Sherlock, H. Reimann, L. M. Konzelman, E. P. Shapiro, B. W. Pettersen, H. Schneider, and N. Sperber, *J. Med. Chem.*, 1963, **6**, 122.

3. (a) E. Goffin, P. Fraikin, D. Abboud, P. de Tullio, C. Beaufour, I. Botez, J. Hanson, L. Danober, P. Francotte, and B. Pirotte, *Eur. J. Med. Chem.*, 2023, **250**, 115221; (b) G. Puja, F. Ravazzini, G. Losi, R. Bardoni, U. M. Battisti, C. Citti, and G. Cannazza, *J. Physiol. Pharmacol.*, 2022, **73**, 19; (c) T. Drapier, P. Geubelle, C. Bouckaert, L. Nielsen, S. Laulumaa, E. Goffin, S. Dilly, P. Francotte, J. Hanson, L. Pochet, J. S. Kastrup, and B. Pirotte, *J. Med. Chem.*, 2018, **61**, 5279; (d) E. Goffin, T. Drapier, A. P. Larsen, P. Geubelle, C. P. Ptak, S. Laulumaa, K. Rovinskaja, J. Gilissen, P. de Tullio, L. Olsen, K. Frydenvang, B. Pirotte, J. Hanson, R. E. Oswald, J. S. Kastrup, and P. Francotte, *J. Med. Chem.*, 2018, **61**, 251; (e) U. M. Battisti, C. Citti, G. Rastelli, L. Pinzi, G. Puja, F. Ravazzini, G. Ciccarella, D. Braghiroli, and G. Cannazza, *MedChemComm*, 2016, **7**, 2410; (f) A. P. Larsen, P. Francotte, K. Frydenvang, D. Tapken, E. Goffin, P. Fraikin, D. H. Caignard, P. Lestage, L. Danober, B. Pirotte, and J. S. Kastrup, *ACS Chem. Neurosci.*, 2016, **7**, 378; (g) U. M. Battisti, K. Jozwiak, G. Cannazza, G. Puia, G. Stocca, D. Braghiroli, C. Parenti, L. Brasili, M. M. Carrozzo, C. Citti, and L. Troisi, *ACS Med. Chem. Lett.*, 2012, **3**, 25; (h) P. Francotte, P. De Tullio, E. Goffin, G. Dintilhac, E. Graindorge, P. Fraikin, P. Lestage, L. Danober, J. Y. Thomas, D. H. Caignard, and B. Pirotte, *J. Med. Chem.*, 2007, **50**, 3153; (i) D. Braghiroli, G. Puia, G. Cannazza, A. Tait, C. Parenti, G. Losi, and M. Baraldi, *J. Med. Chem.*, 2002, **45**, 2355; (j) D. Phillips, J. Sonnenberg, A. C. Arai, R. Vaswani, P. O. Krutzik, T. Kleisli, M. Kessler, R. Granger, G. Lynch, and A. Richard Chamberlin, *Bioorg. Med. Chem.*, 2002, **10**, 1229.
4. (a) Y. Xing, F. Dong, X. Yin, L. Wang, S. Li, *Asian J. Org. Chem.*, 2020, **9**, 1787; (b) J. Sun, T. Tao, D. Xu, H. Cao, Q. Kong, X. Wang, Y. Liu, J. Zhao, Y. Wang, and Y. Pan, *Tetrahedron Lett.*, 2018, **59**, 2099; (c) S. D. Dindulkar, K. T. Lim, B. K. Cho, and Y. T. Jeong, *Phosphorus, Sulfur Silicon Relat. Elem.*, 2014, **189**, 40; (d) D. Zhao, Y.-R. Zhou, Q. Shen, and J.-X. Li, *RSC Adv.*, 2014, **4**, 6486; (e) H. Hikawa, N. Matsuda, H. Suzuki, Y. Yokoyama, and I. Azumaya, *Adv. Synth. Catal.*, 2013, **355**, 2308.
5. (a) C. S. Keenan and S. S. Murphree, *Synth. Commun.*, 2017, **47**, 1085; (b) H. K. Kadam and S. G. Tilve, *RSC Adv.*, 2015, **5**, 83391; (c) K. Ramadas and N. Srinivasan, *Synth. Commun.*, 1992, **22**, 3189.
6. (a) K. Kaneda, R. Naruse, S. Yamamoto, and T. Satoh, *Asian J. Org. Chem.*, 2018, **7**, 793; (b) K. Kaneda, R. Naruse, and S. Yamamoto, *Org. Lett.*, 2017, **19**, 1096.
7. (a) B. N. Patil, J. J. Lade, A. S. Karpe, B. Pownthurai, K. S. Vadagaonkar, V. Mohanasrinivasan, and A. C. Chaskar, *Tetrahedron Lett.*, 2019, **60**, 891; (b) M. Nazari, M. Nematpour, E. Rezaee, M. Jahani, and S. A. Tabatabai, *J. Sulfur Chem.*, 2018, **39**, 646; (c) P. A. Sathe, K. S. Vadagaonkar, M. V. Vhatkar, L. Melone, and A. C. Chaskar, *ChemistrySelect*, 2018, **3**, 277; (d) M. Nematpour, E. Rezaee, M. Jahani, and S. A. Tabatabai, *Tetrahedron Lett.*, 2018, **59**, 2054; (e) K. C. Majumdar and S. Ganai, *Beilstein J. Org. Chem.*, 2013, **9**, 503; (f) J. Restrepo, J. Salazar, and S. E. López, *Phosphorus, Sulfur Silicon Relat. Elem.*, 2011, **186**, 2311; (g) D. Yang, H. Liu, H. Yang, H. Fu, L. Hu, Y. Jiang, and Y. Zhao, *Adv.*

Synth. Catal., 2009, **351**, 1999; (h) D. Yang, H. Fu, L. Hu, Y. Jiang, and Y. Zhao, *J. Comb. Chem.*, 2009, **11**, 653; (i) W. Zhong, X. Chen, and Y. Zhang, *J. Chem. Res. (S)*, 2000, 292.

8. (a) H. Wang, X. Cao, F. Xiao, S. Liu, and G. J. Deng, *Org. Lett.*, 2013, **15**, 4900; (b) M. de F. Pereira and V. Thiéry, *Org. Lett.*, 2012, **14**, 4754; (c) C. L. Yoo, J. C. Fettinger, and M. J. Kurth, *J. Org. Chem.*, 2005, **70**, 6941.
9. (a) M. Badolato, F. Aiello, and N. Neamati, *RSC Adv.*, 2018, **8**, 20894; (b) T. Yamaguchi, K. Sakairi, E. Yamaguchi, N. Tada, and A. Itoh, *RSC Adv.*, 2016, **6**, 56892; (c) Z. B. Xie, S. G. Zhang, G. F. Jiang, D. Z. Sun, and Z. G. Le, *Green Chem. Lett. Rev.*, 2015, **8**, 95; (d) D. Zhao, T. Wang, and J. X. Li, *Chem. Commun.*, 2014, **50**, 6471; (e) X. Fan, B. Li, S. Guo, Y. Wang, and X. Zhang, *Chem. Asian J.*, 2013, **9**, 739; (f) M. Sharif, J. Opalach, P. Langer, M. Beller, and X.-F. Wu, *RSC Adv.*, 2014, **4**, 8; (g) W. H. Correa, S. Papadopoulos, P. Radnidge, B. A. Roberts, and J. L. Scott, *Green Chem.*, 2002, **4**, 245.
10. (a) H. H. Nguyen-Tran, G. W. Zheng, X. H. Qian, and J. H. Xu, *Chem. Commun.*, 2014, **50**, 2861; (b) A. K. Shil and P. Das, *Green Chem.*, 2013, **15**, 3421; (c) S. Liu, Y. Wang, J. Jiang, and Z. Jin, *Green Chem.*, 2009, **11**, 1397; (d) M. Bartra, P. Romea, F. Urpí, and J. Vilarrasa, *Tetrahedron*, 1990, **46**, 587.