

## NEW MACROCYCLIC COMPOUNDS, A PROCESS FOR THEIR PREPARATION AND PHARMACEUTICAL COMPOSITIONS CONTAINING THEM

5 The present invention relates to new macrocyclic compounds, to a process for their preparation and to pharmaceutical compositions containing them.

The compounds of the present invention are new and have very valuable pharmacological characteristics.

### BACKGROUND OF THE INVENTION

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Nuclear factor erythroid 2-related factor 2 (Nrf2), also known as nuclear factor erythroid-derived 2-like 2, is a transcription factor that in humans is encoded by the NFE2L2 gene (Moi P, Chan K, Asunis I, Cao A, Kan YW 1994.. Proceedings of the National Academy of Sciences of the United States of America. 91 (21): 9926–30). Nrf2 is a basic leucine zipper (bZIP) protein  
15 that regulates and coordinates the basal and stress-inducible activation of a vast array of cytoprotective genes. Of particular importance in this regard is the transcription of components of the glutathione and thioredoxin antioxidant systems, as well as enzymes involved in phase I and phase II detoxification of exogenous and endogenous products, NADPH regeneration, and heme metabolism. As such, Nrf2 represents a crucial regulator of the cellular defense  
20 mechanisms against xenobiotic and oxidative stress (Vomund S, Schäfer, A, Parnham MJ, Brüne B, and von Knethen A Int J Mol Sci. 2017 Dec; 18(12): 2772; Bischof LJM, Isoude A. Kuijper1 Schimming JP, Wolters L, ter Braak B, Langenberg JP, Noort D, Beltman JB and van de Water B Archives of Toxicology (2019) 93:435–451). Of similar importance, Nrf2 is involved and modulating crucial cellular processes such as inflammation, autophagy, glucose  
25 and lipid metabolism, stem cell quiescence, and the unfolded protein response (reviewed in Yamamoto M, Kensler TW, Motohashi H (2018). Physiol Rev 98:1169–1203; Ahmed SMU, Luo L, Namani A, Wang XJ, Tang X Biochimica et Biophysica Acta 1863 (2017) 585–597; Hayes JD and Dinkova-Kostova AT, Trends in Biochemical Sciences, vol. 39, no. 4, pp. 199–218, 2014).

30 Since alterations of these fundamental physiological processes are closely link to numerous diseases, the regulatory system of Nrf2 activity turned out to be an attractive drug target for a number of important medical indications such as metabolic, cardiovascular, neurodegenerative

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and autoimmune diseases (reviewed in Cuadrado A, Rojo AI, Wells G, Hayes JD, Cousin SP, Rumsey WL, ttucks OC, Franklin S, Levonen A-L, Kensler TW and Dinkova-Kostova AT Nature Reviews Drug Discovery 2019 volume 18, pages 295–317; Robledinos-Antón N, Fernández-Ginés R, Manda G, Cuadrado A. Oxid Med Cell Longev. 2019;9372182; Satta S, Mahmoud AM, Wilkinson FL, Alexander MY and White SJ. Oxidative Medicine and Cellular Longevity Volume 2017; Gao B., Doan A., Hybertson B.M. Clin. Pharmacol. 2014;6:19–34).

Nrf2 is a crucial part of an evolutionarily conserved defense mechanism in mammals, and zebrafish, fruit fly and *Caenorhabditis elegans* have been shown to have similar anti-stress systems (reviewed by Fuse Y and Kobayashi M. Molecules. 2017 Mar; 22(3): 436). Nrf2 is ubiquitously and constitutively expressed in cells, thus ensuring their prompt protective response to oxidative, inflammatory, and metabolic stresses. The expression of Nrf2 is tightly regulated and under healthy/non-stressed conditions, low Nrf2 levels provide basal expression of its target genes. Under these conditions Nrf2 has a rapid turnover due to its constant degradation by the ubiquitin proteasome system (McMahon M, Thomas N, Itoh K, Yamamoto M, and Hayes JD, Journal of Biological Chemistry 2004 vol. 279, no. 30, pp. 31556–31567; Katoh Y, Iida K, Kang MI, Kobayashi A, Mizukami M, Tong KI, McMahon M, Hayes JD, Itoh K, Yamamoto M. Archives of Biochemistry and Biophysics, vol. 433, no. 2, pp. 342–350, 2005).

Degradation of Nrf2 is regulated through binding to KEAP1 (Kelch-like ECH-associated protein 1), an adapter protein of E3 ubiquitin ligase. In the presence of oxidative and xenobiotic stresses, Nrf2 degradation is blocked through liberation of Keap1, allowing Nrf2 accumulation and its translocation into the nucleus where it forms heterodimers with bZip proteins like small muscle aponeurosis fibromatosis (MAF) K, G, and F via the Neh1 containing CNC–bZIP domain (Ma Q. Annual Review of Pharmacology and Toxicology, vol. 53, no. 1, pp. 401–426, 2013; Hayes JD and Dinkova-Kostova AT, Trends in Biochemical Sciences, vol. 39, no. 4, pp. 199–218, 2014). In humans, these heterodimers directly regulate the expression of about 250 genes that present a regulatory enhancer sequence termed Antioxidant Response Element (ARE). These genes participate and regulate multiple homeostatic functions including redox homeostasis, detoxification, inflammation, proteostasis and metabolism (Pajares M, Jiménez-Moreno N,

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García-Yagüe AJ et al., *Autophagy* 2016, vol. 12, no. 10, pp. 1902–1916; Pajares M, Cuadrado A, and Rojo AI, *Redox Biology*, 2017 vol. 11, pp. 543–553; Pajares M, Jiménez-Moreno N, Dias IHK et al., *Redox Biology* 2015, vol. 6, pp. 409–420; de la Vega MR, Dodson M, Gross C et al. *Current Pharmacology Reports*, vol. 2, no. 2, pp. 91–101, 2016).

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KEAP1 harbors two discrete structural domains, the BTB (broad complex, tramtrack and bric-a-brac) domain in the N-terminal region and the double glycine repeat (DGR; also called the Kelch domain) in the C-terminal region (Itoh K, Wakabayashi N, Katoh Y, Ishii T, Igarashi K, Engel JD and Yamamoto M *Genes Dev.* 1999 Jan 1; 13(1): 76–86). While the BTB domain contributes to the homodimerization of KEAP1 and its interaction with CUL3, the Kelch domain mediates KEAP1 binding to Nrf2 by interacting with the Neh2 domain. In this KEAP1–Nrf2 interaction, two specific motifs in the Neh2 domain of Nrf2, namely DLG and ETGE, individually bind to the Kelch domains of the KEAP1 homodimer. Identification of the two-site binding of the KEAP1 homodimer to Nrf2 led to propose the molecular mechanism of electrophilic stress sensing which has been described in detail by Tong et al. (Tong KI, Katoh Y, Kusunoki H, Itoh K, Tanaka T, Yamamoto M (2006) *Mol Cell Biol* 26:2887–2900; Tong KI, Padmanabhan B, Kobayashi A, Shang C, Hirotsu Y, Yokoyama S, Yamamoto M (2007). *Mol Cell Biol* 27:7511–7521. <https://doi.org/10.1128/MCB.00753-072006>) and reviewed in Yamamoto et al. (Yamamoto M, Kensler TW, Motohashi H (2018). *Physiol Rev* 98:1169–1203).

The intervening region (IVR) of KEAP1 resides between the BTB and the DGR/Kelch domains and is rich in reactive cysteine (Cys) residues that function as stress sensors. Twenty-seven and twenty-five Cys residues were identified in the human and mouse KEAP1 proteins, respectively. Among these, Cys151 in BTB domain and Cys273/288 in IVR are major sensor cysteine residues (Dinkova-Kostova, A.T., Holtzclaw, W.D., Cole, R.N., Itoh, K., Wakabayashi, N., Katoh, Y., Yamamoto, M., and Talalay, P. (2002). *Proc. Natl. Acad. Sci. USA* 99, 11908–11913; Zhang, D.D. and Hannink, M. (2003) *Mol. Cell. Biol.* 23, 8137–8151; Saito, R., Suzuki, T., Hiramoto, K., Asami, S., Naganuma, E., Suda, H., Iso, T., Yamamoto, H., Morita, M., Baird, L., et al. (2016). *Mol. Cell. Biol.* 36,271–284; Suzuki T, Muramatsu A, Saito R, Iso T, Shibata T, Kuwata K, Kawaguchi SI, Iwawaki T, Adachi S, Suda H, Morita M, Uchida K, Baird L,

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Yamamoto M (2019) Cell Rep 28:746-758). The specificity of Keap1 cysteine residues against various chemical inducers of Nrf2 was investigated by using mutants of three major cysteine residues namely Cys 151, Cys273 and Cys288. These experiments led to the classification of Nrf2 inducers into four classes, namely class I (Cys151 preferring), class II (Cys288 preferring),  
5 class III (Cys151/Cys273/Cys288 collaboration preferring) and class IV (Cys151/Cys273/Cys288 independent) (Saito, R., Suzuki, T., Hiramoto, K., Asami, S., Naganuma, E., Suda, H., Iso, T., Yamamoto, H., Morita, M., Baird, L., et al. (2016). Mol. Cell. Biol. 36,271–284). The cysteine code of Keap1 modification sites with various electrophiles has been summarized recently (Unoki T, Akiyama M, Kumagai Y. Int J Mol Sci. 2020 Jan 15;21(2)).  
10 It appears, however, challenging to define the chemical properties of each class as exemplified by 15-deoxy-prostaglandin J2 (15d-PGJ2) and prostaglandinA2 (PGA2). Despite sharing similar structural characteristics, 15d-PGJ2 and PGA2 belong to class II and class IV, respectively. Therefore, the complex properties such as structure and reactivity of electrophiles may determine the interaction with specific Keap1 reactive cysteine residues (Unoki T,  
15 Akiyama M, Kumagai Y. Int J Mol Sci. 2020 Jan 15;21(2)).

Nrf2 activators, or KEAP1 inhibitors as their molecular target is KEAP1 (Magesh S., Chen Y. and Hu L. Medicinal Research Reviews, 2012 vol. 32, no. 4, pp. 687–726), can be classified as electrophiles, protein-protein interaction (PPI) inhibitors, and multi target drugs.  
20 Most pharmacological Nrf2 activators are electrophilic molecules that covalently modify one or more cysteine residues present in the thiol-rich KEAP1 protein by oxidation or alkylation (Hur W., Gray N. S. Current Opinion in Chemical Biology. 2011;15(1):162–173; Satoh T., McKercher S. R., Lipton S. A. Free Radical Biology & Medicine. 2013;65:645–657; Wilson A. J., Kerns J. K., Callahan J. F., Moody C. J. Journal of Medicinal Chemistry. 2013;56(19):7463–  
25 7476). The only marketed Nrf2 activators to date are dimethyl fumarate (BG-12 or Tecfidera) and diroximel fumarate (DRF) from Biogen. Dimethyl fumarate as been approved in 2013 and DRF in 2019 for relapsing-remitting multiple sclerosis (MS) (Schimrigk S., Brune N., Hellwig K., et al. European Journal of Neurology. 2006;13(6):604–610; Gold R., Kappos L., Arnold D. L., et al. The New England Journal of Medicine. 2012;367(12):1098–1107; Fox R. J., Miller D.  
30 H., Phillips J. T., et al. The New England Journal of Medicine. 2012;367(12):1087–1097; Xu



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Z., Zhang F., Sun F., Gu K. F., Dong S., He D. Cochrane Database of Systematic Reviews. 2015;4; Mills E. A., Ogrodnik M. A., Plave A., Mao-Draayer Y. Frontiers in Neurology. 2018;9(5)). Previously, dimethyl fumarate was authorized for the treatment of psoriasis (Hoxtermann S., Nuchel C., Altmeyer P. Dermatology. 1998;196 (2):223–230). The dimethyl fumarate-induced activation of Nrf2 in the central nervous system was described in the MS mice model of experimental allergic encephalomyelitis (Linker R. A., Lee D. H., Ryan S., et al. Brain. 2011;134(3):678–692). In this model, dimethyl fumarate -dependent Nrf2 activation correlated with an improvement in the clinical course of MS, favored axon preservation, and increased astrocyte activation. These beneficial effects of dimethyl fumarate did not occur in Nrf2-null mice, hence indicating that dimethyl fumarate was acting mainly by targeting the Nrf2 pathway. dimethyl fumarate is mostly converted to monomethyl fumarate (MMF) by intestinal esterases, and only a small fraction of dimethyl fumarate is found in blood conjugated with glutathione (Dibbert S., Clement B., Skak-Nielsen T., Mrowietz U., Rostami-Yazdi M. Archives of Dermatological Research. 2013;305(5):447–451). Since MMF is considered the active metabolite of dimethyl fumarate, several clinical trials are ongoing to assess the efficacy and safety of MMF.

Nrf2 activators interacting with the cysteine residues of Keap1 by virtue of their electrophilic nature inherently also react with glutathione or thiol in proteins. Since such thiol-reactive chemicals have the potential to cause electrophilic damage in cells, chemicals that directly inhibit the protein-protein interaction (PPI) of Keap1 and Nrf2 are emerging as attractive novel Nrf2 inducers (Bertrand, H. C., Schaap, M., Baird, L., Georgakopoulos, N. D., Fowkes, A., Thiollier, C., Kachi, H., Dinkova-Kostova, A. T., and Wells, G. (2015). J. Med. Chem. 58, 7186–7194; Davies, T. G., Wixted, W. E., Coyle, J. E., Griffiths-Jones, C., Hearn, K., McMenamin, R., Norton, D., Rich, S. J., Richardson, C., Saxty, G., Willems, H. M., Woolford, A. J., Cottom, J. E., Kou, J. P., Yonchuk, J. G., et al. (2016). J. Med. Chem. 59, 3991–4006; Jiang, ZY, Lu, M C., and You, Q. D. (2016). J. Med. Chem. 59, 10837–10858; Lu, M. C., Ji, J. A., Jiang, Y. L., Chen, Z. Y., Yuan, Z. W., You, Q. D., and Jiang, Z. Y. (2016). Sci. Rep. 6, 26585; Yasuda, D., Nakajima, M., Yuasa, A., Obata, R., Takahashi, K., Ohe, T., Ichimura, Y., Komatsu, M., Yamamoto, M., Imamura, R., Kojima, H., Okabe, T., Nagano, T., and Mashino, T. (2016) Bioorg. Med. Chem. Lett. 26, 5956–5959).

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PPI inhibitors interfere with the docking of Nrf2 to the Kelch propeller of KEAP1 and most likely provide more selectivity over electrophilic compounds (Richardson B. G., Jain A. D., Speltz T. E., Moore T. W. *Bioorganic & Medicinal Chemistry Letters*. 2015;25(11):2261–  
5 2268). Based on the X-ray crystal structure of KEAP1, small PPI inhibitors have been designed to impede the binding of the DLG and ETGE motifs to KEAP1. The ETGE motif adopts a  $\beta$ -hairpin structure that docks to the Kelch propeller of KEAP1 through specific hydrophobic and electrostatic interactions (Padmanabhan B., Tong K. I., Ohta T., et al. *Molecular Cell*. 2006;21(5):689–700; Lo S. C., Li X., Henzl M. T., Beamer L. J., Hannink M. *The EMBO*  
10 *Journal*. 2006;25(15):3605–3617). Up-to-date, no PPI inhibitor has entered clinical development, however, potent and selective PPI inhibitors of the KEAP1 Kelch–Nrf2 interaction have been described and their activity was confirmed in *in vitro* and *in vivo* studies, respectively (Davies, T. G., Wixted, W. E., Coyle, J. E., Griffiths-Jones, C., Hearn, K., McMenamin, R., Norton, D., Rich, S. J., Richardson, C., Saxty, G., Willems, H. M., Woolford, A. J., Cottom, J.  
15 E., Kou, J. P., Yonchuk, J. G., et al. (2016). *J. Med. Chem.* 59, 3991–4006; Jiang, ZY, Lu, M C., and You, Q. D. (2016). *J. Med. Chem.* 59, 10837–10858; Robledinos-Antón N, Fernández-Ginés R, Manda G, Cuadrado A. *Oxid Med Cell Longev*. 2019:9372182).

Another mechanism of KEAP1 inhibition is related to the interaction with the CUL3/RBX1  
20 complex, which is required for Nrf2 ubiquitination and degradation. Cys-151 located at the BTB domain influences the interaction of KEAP1 with CUL3. The crystal structure of the BTB domain bound to the pentacyclic triterpenoid 2-cyano-3,12-dioxo-oleana-1,9(11)-dien-28-oate (Bardoxolone, CDDO-Me or RTA 402) indicates that adduct formation with Cys-151 disrupts the interaction between KEAP1 and CUL3 (Cleasby A., Yon J., Day P. J., et al. *Structure of the*  
25 *BTB domain of Keap1 and its interaction with the triterpenoid antagonist CDDO*. *PLoS One*. 2014;9 (6, article e98896); Iso T., Suzuki T., Baird L., Yamamoto M. *Molecular and Cellular Biology*. 2016;36(24): 3100–3112; Dayalan Naidu S., Muramatsu A., Saito R., et al. *Scientific Reports*. 2018;8(1):p. 8037). As a result, KEAP1 is locked in a Nrf2 bound conformation and newly expressed Nrf2 thereby escapes KEAP1-CUL3-mediated ubiquitination.

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Bardoxolone entered clinical trials for the treatment of advanced chronic kidney disease (CKD) and type 2 diabetes mellitus (Pergola P. E., Raskin P., Toto R. D., et al. The New England Journal of Medicine. 2011;365(4):327–336). Although phase II clinical trials demonstrated long-term increment in glomerular filtration, the compound was halted at phase III due to cardiovascular safety issues (Zhang D. D. Antioxidants & Redox Signaling. 2013;19(5):517–518. doi: 10.1089/ars.2012.5118). A new phase III clinical trial of Bardoxolone in patients with diabetic kidney disease (AYAME study) has recently started by Kyowa Kirin to better define the safety and efficacy profiles of CDDO-Me. Currently, Bardoxolone is also in clinical studies for the Alport syndrome (phase 2/3 CARDINAL trial) and pulmonary hypertension (phase 3 CATALYST trial). Furthermore, Reata is developing Bardoxolone in rare forms of CKD including autosomal dominant polycystic kidney disease (ADPKD), IgA nephropathy (IgAN), type 1 diabetic CKD (T1D CKD), and focal segmental glomerulosclerosis (FSGS). A second-generation derivative of Bardoxolone, called Omaveloxone (RTA-408), is under clinical investigation in the pivotal, registration, MOXIe trial for Friedreich's ataxia (Lynch D. R., Farmer J., Hauser L. et al. Annals of Clinical Translational Neurology. 2019;6(1):15–26; <https://www.reatapharma.com/our-science/pipeline/>).

Several additional mechanisms have been proposed to explain the dissociation of Nrf2 from Keap1 under stress conditions. In addition to oxidation of the cysteine residues of Keap1 and targeting the DLG and ETGE binding sites, the binding of p62 to Keap1 and phosphorylation of Nrf2 by GSK3 have received particular attention.

p62, also known as sequestosome 1 (SQSTM1), is a ubiquitin-binding protein that targets protein aggregates for degradation via the autophagic pathway. p62 competes with Nrf2 for binding to Keap1, and binding of p62 to Keap1 leads to the degradation of Keap1 and the consequent Nrf2 stabilization (Komatsu M, Kurokawa H, Waguri S, Taguchi K, Kobayashi A, Ichimura Y, et al. Nat Cell Biol 2010; 12(3):213–23; Lau A, Wang XJ, Zhao F, Villeneuve NF, Wu T, Jiang T, et al. Mol Cell Biol 2010; 30(13):3275–85). The p62 gene promoter contains an ARE and creates a Nrf2 driven positive feedback loop by inducing ARE-driven p62 gene transcription (Jain A, Lamark T, Sjøttem E, Larsen KB, Awuh JA, Overvatn A, et al. J Biol Chem 2010; 285(29):22576–91). Since p62 is a cargo receptor for selective autophagy, Keap1-

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Nrf2 has an intriguing functional interaction with autophagy (Towers CG, Fitzwalter BE, Regan D, Goodspeed A, Morgan MJ, Liu CW, et al. *Dev Cell* 2019. 23;50(6):690-703. doi: 10.1016/j.devcel.2019.07.010).

Nrf2 stability is regulated also by glycogen synthase kinase (GSK)-3 mediated phosphorylation.

- 5 GSK-3 phosphorylates the DSGIS motif located in the Neh6 domain of Nrf2 and thereby creates a recognition site for  $\beta$ -transducin repeats containing E3 ubiquitin protein ligase ( $\beta$ -TrCP). This interaction targets Nrf2 to ubiquitin-dependent proteasome degradation (Rada P1, Rojo AI, Chowdhry S, McMahon M, Hayes JD, Cuadrado A. *Mol Cell Biol.* (2011) Mar;31(6):1121-33). These data may suggest that GSK-3 inhibitors have utility as Nrf2 activators.

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Besides dimethyl fumarate for the treatment of relapsing-remitting multiple sclerosis and psoriasis, respectively, the broad therapeutic potential of Nrf2 activators are supported by a number of studies.

- 15 The importance of Nrf2 in protection against reactive electrophiles was first demonstrated using acetaminophen. Nrf2 knockout mice displayed greater hepatotoxicity, manifested in increased serum ALT values and altered hepatic histology, following acetaminophen exposure, relative to WT mice (Chan K, Han X, Kan Y. *Proc Natl Acad Sci U S A* 2001;98:4611–4616; Enomoto A, Itoh K, Nagayoshi E, Haruta J, Kimura T, O'Connor T, Harada T, Yamamoto M. *Toxicol Sci* 2001;59:169–177).

- 20 Acetaminophen was also shown to activate the nuclear translocation of Nrf2 at non-toxic doses thereby illustrating the role of Nrf2 in coordinating an adaptive response leading to attenuated acetaminophen toxicity (Goldring C, Kitteringham N, Elsby R, Randle L, Clement Y, Williams D, McMahon M, Hayes J, Itoh K, Yamamoto M, Park B. *Hepatology* 2004;39:1267–1276). This adaptive response resulted in increased de novo synthesis of GSH and conjugation and excretion of reactive acetaminophen metabolites. This observation was further confirmed by the use of hepatocyte-specific conditional Keap1 knockout mice, a model in which the inhibitory component of the Nrf2 signaling pathway is absent resulting in elevated and sustained nuclear accumulation of Nrf2. These conditional knockout mice were considerably more resistant to
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- 30 acetaminophen toxicity than WT mice due to higher levels of Nrf2-regulated cytoprotective

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enzymes (Okawa H, Motohashi H, Kobayashi A, Aburatani H, Kensler T, Yamamoto M. *Biochem Biophys Res Commun* 2006;339:79–88).

Activation of Nrf2 signaling by KEAP1 gene knockdown suppressed the onset of diabetes and  
5 when crossed with diabetic db/db mice, blood glucose levels became lower through  
improvement of both insulin secretion and insulin resistance. KEAP1 knockdown also  
prevented high-calorie-diet-induced diabetes and oral administration of the Nrf2 inducer  
CDDO-Im also attenuated diabetes in db/db mice. Interestingly, Nrf2 induction altered  
antioxidant-, energy consumption-, and gluconeogenesis-related gene expression in metabolic  
10 tissues. Overall, these data suggest that KEAP1-Nrf2 system is a critical target for preventing  
the onset of diabetes mellitus (Urano A, Furusawa Y, Yagishita Y, Toshiaki Fukutomi T,  
Muramatsu H, Negishi T, Sugawara A, Kensler TW, Yamamoto M. *Molecular and Cellular  
Biology* 2013; 29:296–3010). In line with data obtained in db/db mice, Xue and colleagues  
investigated the impact of Nrf2 ablation in ob/ob mice. Global ablation led to reduced white  
15 adipose tissue (WAT) mass, but resulted in an even more severe metabolic syndrome with  
aggravated insulin resistance, hyperglycemia, and hypertriglyceridemia. Compared with wild-  
type mice, WAT of ob/ob mice expressed substantially higher levels of many genes related to  
antioxidant response, inflammation, adipogenesis, lipogenesis, glucose uptake, and lipid  
transport. Absence of Nrf2 in WAT resulted in reduced expression of most of these factors at  
20 mRNA or protein levels. These findings support a role for Nrf2 in regulating adipose  
development and function, by which Nrf2 controls the capacity of WAT expansion and insulin  
sensitivity and maintains glucose and lipid homeostasis (Xue P, Hou Y, Chen Y, Yang B, Fu J,  
Zheng H, Yarborough K, Woods CG, Liu D, Yamamoto M, Zhang Q, Andersen ME, Pi J.  
*Diabetes*. 2013 Mar;62(3):845-54).

25 Recent data support a critical role of Nrf2 in  $\beta$ -cell survival and proliferation under stress  
conditions. Induction of Nrf2 is required for ChREBP $\alpha$ -mediated mitochondrial biogenesis and  
for glucose-stimulated and ChREBP $\alpha$ -augmented  $\beta$ -cell proliferation. Interestingly,  
overexpression of Nrf2 was sufficient to drive human  $\beta$ -cell proliferation in vitro, confirming  
the critical role of this pathway and its potential utility for therapeutic  $\beta$ -cell regeneration  
30 strategies (Kumar A, Katz LS, Schulz AM, Kim M, Honig LB, Li L, Davenport B, Homann D,

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- Garcia-Ocaña A, Herman MA, Haynes CM, Chipuk JE, Scott DK. Diabetes. 2018 Aug;67(8):1561-1575). Furthermore, Nrf2 activators like Oltipraz or dimethyl fumarate protect isolated mouse beta cells against glucolipotoxicity by preserving mitochondrial function, glucose-dependent ROS turnover, and antagonizing glucolipotoxicity-induced inhibition of insulin release and apoptosis (Schultheis J, Beckmann D, Mulac D, Müller L, Esselen M, Düfer M. Oxid Med Cell Longev. 2019 Nov 11;2019:7518510).
- An important role of Nrf2 in preventing the onset of type 2 diabetes in humans is supported by the identification of the Nrf2 rs6721961 polymorphism, a variant of the Nrf2 gene in the upstream promoter region. In a Chinese cohort this polymorphism is significantly associated with oxidative stress, anti-oxidative status, and risk of newly-diagnosed T2DM (Wang X, Chen H, Liu J, Ouyang Y, Wang D, Bao W and Liu L. Int J Mol Sci. 2015; 16(7): 16483–16496). The SNP rs6721961, was initially identified to be associated with the risk of acute lung injury, an oxidative stress-mediated condition (Marzec J.M., Christie J.D., Reddy S.P., Jedlicka A.E., Vuong H., Lanken P.N., Aplenc R., Yamamoto T., Yamamoto M., Cho H.-Y. FASEB J. 2007;21:2237–2246).
- Nrf2 activation in the type 1 diabetes NOD mouse model by knocking down the expression of Keap1, inhibited T-cell infiltration within the islets, ameliorated impairment of insulin secretion and prevented the development of diabetes mellitus. Notably, Nrf2 activation decreased both the plasma interferon- $\gamma$  (IFN- $\gamma$ ) levels and the IFN- $\gamma$ -positive cell numbers in the pancreatic islets, demonstrating that activation of Nrf2 signaling prevented the onset of type 1 diabetes mellitus in NOD mice. Thus, Nrf2 appears to be a potential target for the prevention and treatment of type 1 diabetes (Yagishita Y. et al. J Endocrinol. : JOE-18-0355.R2. Published online 2019 Jan 1. doi: 10.1530/JOE-18-0355).
- Oxidative stress and inflammation are the most important pathogenic events in the development and progression of liver diseases and multiple studies have shown that activation or suppression of Nrf2 significantly affects the progression of liver diseases (Xu D, Xu M, Jeong S, Qian Y, Wu H, Xia Q and Kong X. Front Pharmacol. 2018; 9: 1428). Nrf2 has been found to be a key regulator to protect against the development of NASH (Gupte A. A., Lyon C. J., Hsueh W. A. (2013).. Curr. Diabetes Rep. 13 362–371. 10.1007/s11892-013-0372-1), and conversely, loss or

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deletion of Nrf2 has been found to cause benign steatosis that progresses to NASH and contributes to the exacerbation of disease status (Chowdhry S., Nazmy M. H., Meakin P. J., Dinkova-Kostova A. T., Walsh S. V., Tsujita T., et al. (2010). *Free Radic. Biol. Med.* 48 357–371; Wang C., Cui Y., Li C., Zhang Y., Xu S., Li X., et al. (2013). *Lipids Health Dis.* 12:165. 5 10.1186/1476-511X-12-165; Ramadori P., Drescher H., Erschfeld S., Fragoulis A., Kensler T. W., Wruck C. J., et al. (2017). *Oxid. Med. Cell. Longev.* 2017:3420286). NASH development was also investigated in p62:Nrf2 double-knockout (DKO) mice. DKO mice showed massive hepatomegaly and steatohepatitis, hyperphagia-induced obesity coupled with insulin resistance and adipokine imbalance (Akiyama K, Warabi E, Okada K, Yanagawa T, Ishii T, Kose K, 10 Tokushige K, Ishige K, Mizokami Y, Yamagata K, Onizawa K, Ariizumi SI, Yamamoto M, Shoda J. *Exp Anim.* 2018 May 10;67(2):201-218).

A protective role of Nrf2 in NASH has been shown by Sharma and colleagues by using TBE-31, an Nrf2 activating small molecule. Treatment with TBE31 reversed insulin resistance in high fat high fructose fed wild-type mice, but not in Nrf2-null mice. Furthermore, TBE-31 15 treatment mice substantially decreased liver steatosis and expression of lipid synthesis genes, while increasing hepatic expression of fatty acid oxidation and lipoprotein assembly genes. Also, TBE-31 treatment decreased ER stress, expression of inflammation genes, and markers of apoptosis, fibrosis, and oxidative stress in the livers of high fat high fructose fed wild-type mice. By comparison, TBE-31 did not decrease steatosis, ER stress, lipogenesis, inflammation, 20 fibrosis, or oxidative stress in livers of HFFr-fed Nrf2-null mice. The authors concluded that pharmacologic activation of Nrf2 in mice that had already been rendered obese and insulin resistant reversed insulin resistance, suppressed hepatic steatosis, and mitigated against NASH and liver fibrosis. These effects were mainly attributed to inhibition of ER, inflammatory, and oxidative stress (Sharma RS, Harrison DJ, Kisielowski D, Cassidy DM, McNeilly AD, 25 Gallagher JR, Walsh SV, Honda T, McCrimmon RJ, Dinkova-Kostova AT, Ashford MLJ, Dillon JF, Hayes JD *Cell Mol Gastroenterol Hepatol.* 2017 Dec 13;5(3):367-398).

A liver protective role of Nrf2 has also been demonstrated upon acute high doses of alcohol exposure using Nrf2-KO mice. Alcohol treatment resulted in substantially worsened liver and pancreatic injuries as well as pancreatic  $\beta$ -cell injury in these animals (Sun J, Fu J, Zhong Y, Li

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L, Chen C, Wang X, Wang L, Hou Y, Wang H, Zhao R, Zhang X, Yamamoto M, Xu Y, Pi J. Food Chem Toxicol. 2018 Nov;121:495-503).

Nrf2 activators have potential utility for diseases/indications that are linked to increased oxidative stress and inflammation, impaired redox potential, impaired detoxification and  
5 deregulated metabolism.

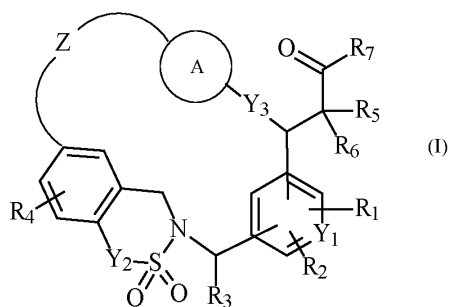
Based on Nrf2 knockout, KEAP1 knockout, genetic polymorphisms and compound mediated Nrf2 activation studies, respectively, evidence is provided for indications including Type I diabetes and Type II diabetes and associated complications such as diabetic cardiomyopathy, diabetic retinopathy, diabetic neuropathy, diabetic nephropathy and diabetic wound healing;  
10 Maternal diabetes; Liver diseases such as Nonalcoholic Steatohepatitis (NASH), Non-Alcoholic Fatty Liver Disease, toxin-induced liver disease (e.g., acetaminophen-induced hepatic disease), Alcoholic Liver Disease (ALD), cholestasis, Primary Sclerosing Cholangitis (PSC), viral hepatitis, cirrhosis, Primary Biliary Cirrhosis (PBC), End Stage Liver Disease, Fibrosis; Kidney diseases such as Chronic kidney disease (CKD), Acute kidney injury, Contrast-induced  
15 nephropathy, Autosomal dominant polycystic kidney disease (ADPKD), Alström and Alport syndromes, sepsis-induced acute kidney injury; kidney disease or malfunction seen during kidney transplantation, focal segmental glomerulosclerosis, IgA glomerulonephritis/nephropathy, fibrosis; Lung diseases such as pulmonary fibrosis, Idiopathic Pulmonary Fibrosis (IPF), cystic fibrosis, Acute lung injury, Lung infection, Chronic  
20 Obstructive Pulmonary Disease (COPD), Emphysema, Pulmonary Arterial Hypertension, Lung disease secondary to environmental exposures, chronic and acute asthma, acute respiratory distress syndrome; Cardiac diseases such as atherosclerosis, hypertension, heart failure, stroke, cardiomyopathy, coronary heart disease, Myocardial Ischemia; Neuronal damage, Traumatic brain injury, Depression, Epilepsy, Hepatic Encephalopathy, Huntington's disease, Parkinson's  
25 disease, Alzheimer's disease, autism, Friedreich's ataxia, Amyotrophic Lateral Sclerosis (ALS), Multiple Sclerosis (MS), Stroke, Cerebral infarction, Encephalopathy, neuronal damage/injury, Spinal cord injury; Inflammatory diseases such as inflammatory bowel disease, Ulcerative Colitis, Crohn's Disease, Pancreatitis, Arthritis, lupus nephritis; Eye diseases such as Age-related macular degeneration (AMD), Ocular Neurodegenerative Diseases, Age-related macular  
30 degeneration, cataracts, glaucoma, eye injury, Fuchs Endothelial Corneal Dystrophy (FECD),



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- uveitis, Optic neuropathy/Ocular Neurodegenerative Diseases; Colon cancer; Autoimmune diseases; Psoriasis, dermatitis/topical effects of radiation, immunosuppression due to radiation exposure, Preeclampsia, High altitude sickness; Wound healing; Metabolic syndrome; Mitochondrial myopathies; Malaria; Ferroptosis/iron overload; Allergic contact dermatitis;
- 5 Alcohol dependence; Amyloidosis; Anemia; Anxiety disorder; Asperger syndrome; Eczema; Brain edema; Brain ischemia; Cerebrovascular disorder; Chronic fatigue syndrome; Cognitive decline; Dermatitis/radiation-induced dermatitis; Duchenne muscular dystrophy; Edema; Encephalitis; Male/female fertility; Fracture healing; Gastroesophageal reflux disease; Hearing loss; influenza infections; Intestinal barrier dysfunction; Osteoarthritis; Osteoporosis;
- 10 Radiation-induced injury; Reflux-Induced Esophagitis; Reperfusion injury (brain, heart, kidney, liver, retina); Schizophrenia; Seizures; Sjogren syndrome; Sickle cell disease; Skin ulcer; Vascular endothelial dysfunction; Blood-brain barrier dysfunction; Down syndrome.
- 15 WO 2015/092713 discloses bis aryl compounds as Nrf2 regulators.

The present invention relates more especially to compounds of formula (I) :

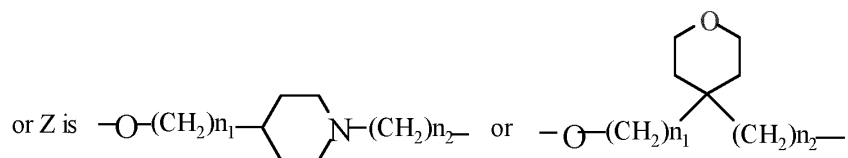
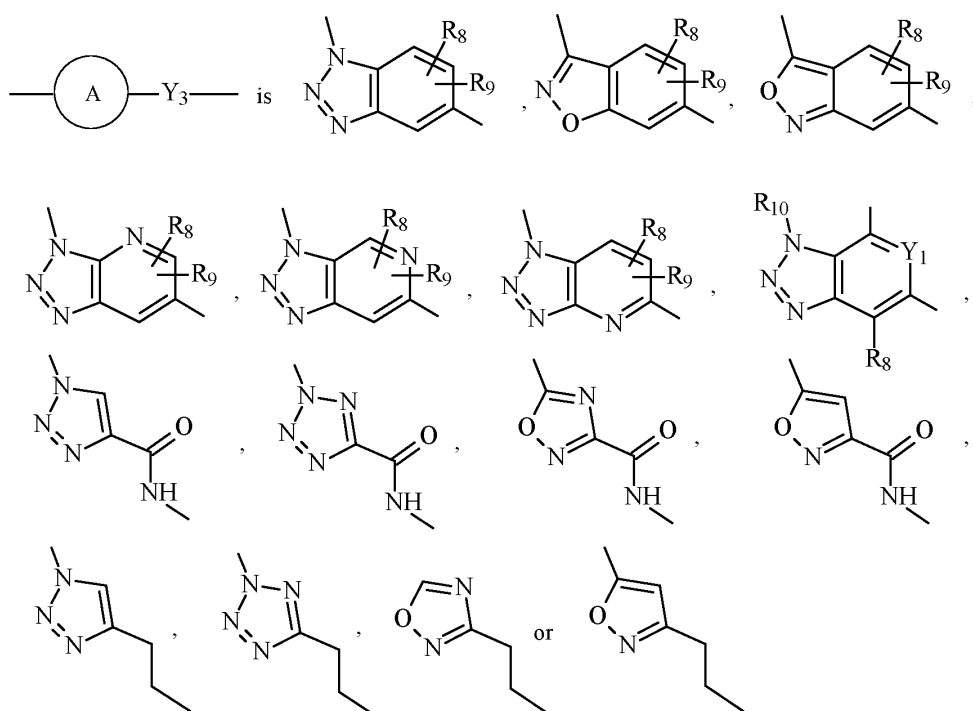


- 20 wherein

Z is -O-(CH<sub>2</sub>)<sub>n1</sub>-, -O-(CH<sub>2</sub>)<sub>n1</sub>-O-(CH<sub>2</sub>)<sub>n2</sub>-, -O-(CH<sub>2</sub>)<sub>n1</sub>-S-(CH<sub>2</sub>)<sub>n2</sub>-, O-(CH<sub>2</sub>)<sub>n1</sub>-S(O)-(CH<sub>2</sub>)<sub>n2</sub>-, O-(CH<sub>2</sub>)<sub>n1</sub>-S(O<sub>2</sub>)-(CH<sub>2</sub>)<sub>n2</sub>-, -O-(CH<sub>2</sub>)<sub>n1</sub>-NR-(CH<sub>2</sub>)<sub>n2</sub>-, -O-(CH<sub>2</sub>)<sub>n1</sub>-CHR'-(CH<sub>2</sub>)<sub>n2</sub>-, -NR-(CH<sub>2</sub>)<sub>n1</sub>-, -NR-(CO)-(CH<sub>2</sub>)<sub>n1</sub>-, -O-(CH<sub>2</sub>)<sub>n1</sub>-Ar-(CH<sub>2</sub>)<sub>n2</sub>-, -O-(CH<sub>2</sub>)<sub>n1</sub>-Ar-O-(CH<sub>2</sub>)<sub>n2</sub>-, -O-(CH<sub>2</sub>)<sub>n1</sub>-Ar-S-(CH<sub>2</sub>)<sub>n2</sub>-, -O-(CH<sub>2</sub>)<sub>n1</sub>-Ar-S(O)-(CH<sub>2</sub>)<sub>n2</sub>-, -O-(CH<sub>2</sub>)<sub>n1</sub>-Ar-S(O<sub>2</sub>)-(CH<sub>2</sub>)<sub>n2</sub>-, -O-(CH<sub>2</sub>)<sub>n1</sub>-Ar-CHR'-(CH<sub>2</sub>)<sub>n2</sub>-, -O-(CH<sub>2</sub>)<sub>n1</sub>-Ar-CH=CH-, O-Ar-NR-(CH<sub>2</sub>)<sub>n1</sub>-, -(CH<sub>2</sub>)<sub>n1</sub>-NR-(CO)-(CH<sub>2</sub>)<sub>n2</sub>-

25

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Y<sub>1</sub> is C or N,Y<sub>2</sub> is O or NR',

5

Ar is an optionally substituted aryl or heteroaryl group

R is a hydrogen atom, a linear or branched C<sub>1</sub>-C<sub>3</sub> alkyl group or an optionally substituted aryl group,R' is a hydrogen atom or a group selected from hydroxyl, optionally substituted aryl and linear or branched C<sub>1</sub>-C<sub>3</sub> alkyl optionally substituted by alkoxy or by one to three halogen atoms,

10

n<sub>1</sub> and n<sub>2</sub> are each an integer from 1 to 6,

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R<sub>1</sub>, R<sub>2</sub>, R<sub>4</sub>, R<sub>8</sub>, R<sub>9</sub>, which may be identical or different, are each a hydrogen atom or a group selected from halo, cyano, linear or branched C<sub>1</sub>-C<sub>3</sub> alkyl optionally substituted by one to three halogen atoms, linear or branched C<sub>1</sub>-C<sub>3</sub> alkoxy or optionally substituted aryl,

R<sub>3</sub> is hydrogen or a linear or branched C<sub>1</sub>-C<sub>3</sub> alkyl group optionally substituted by one to three  
5 halogen atoms,

or R<sub>2</sub> and R<sub>3</sub> together form a ring with the atoms bearing them,

R<sub>5</sub>, R<sub>6</sub>, identical or different, are each a hydrogen, deuterium or halogen atom or a linear or branched C<sub>1</sub>-C<sub>3</sub> alkyl group,

R<sub>7</sub> is a group selected from hydroxyl and NHR'<sub>7</sub>,

10 wherein R'<sub>7</sub> is a linear or branched C<sub>1</sub>-C<sub>6</sub> alkyl group or an optionally substituted aryl or heteroaryl group,

their optical isomers and addition salts thereof with a pharmaceutically acceptable base.

"Aryl group" means a phenyl, naphthyl, or biphenyl group optionally substituted by one or more  
15 identical or different groups selected from halogen, hydroxy, amino, linear or branched (C<sub>1</sub>-C<sub>6</sub>)-alkyl optionally substituted by one to 3 halogen atoms, carboxy, cyano, linear or branched (C<sub>1</sub>-C<sub>6</sub>)-alkoxy optionally substituted by one to 3 halogen atoms, linear or branched (C<sub>1</sub>-C<sub>6</sub>)-aminoalkyl optionally N-substituted by one or two linear or branched (C<sub>1</sub>-C<sub>6</sub>)-alkyl groups, linear or branched (C<sub>1</sub>-C<sub>6</sub>)-alkylsulfanyl optionally substituted by one to 3 halogen atoms, linear or branched (C<sub>1</sub>-C<sub>6</sub>)-  
20 alkylsulfinyl optionally substituted by one to 3 halogen atoms or linear or branched (C<sub>1</sub>-C<sub>6</sub>)-alkylsulfonyl optionally substituted by one to 3 halogen atoms.

"Heteroaryl group" means a monocyclic aromatic group or a bicyclic aromatic or partially aromatic group having from 5 to 12 ring members and containing one, two or three hetero atoms  
25 selected from oxygen, nitrogen and sulphur, it being understood that the heteroaryl may be optionally substituted by one or more identical or different groups selected from halogen, hydroxy, amino, cyano, linear or branched (C<sub>1</sub>-C<sub>6</sub>)-alkyl optionally substituted by one to 3 halogen atoms, linear or branched (C<sub>1</sub>-C<sub>6</sub>)-alkoxy optionally substituted by one to 3 halogen atoms, linear or branched (C<sub>1</sub>-C<sub>6</sub>)-aminoalkyl optionally N-substituted by one or two linear or branched (C<sub>1</sub>-C<sub>6</sub>)-alkyl  
30 groups, linear or branched (C<sub>1</sub>-C<sub>6</sub>)-alkylsulfanyl optionally substituted by one to 3 halogen atoms,

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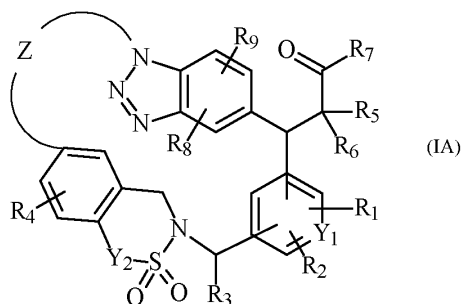
linear or branched (C<sub>1</sub>-C<sub>6</sub>)-alkylsulfinyl optionally substituted by one to 3 halogen atoms or linear or branched (C<sub>1</sub>-C<sub>6</sub>)-alkylsulfonyl optionally substituted by one to 3 halogen atoms.

Among the heteroaryl groups there may be mentioned, without implying any limitation,  
 5 pyrrolyl, furyl, thienyl, thiazolyl, isothiazolyl, oxazolyl, isoxazolyl, pyrazolyl, imidazolyl, pyridinyl (also known as pyridyl), pyrazinyl, pyridazinyl, pyrimidinyl, indolyl, dihydroisindolyl, indazolyl, benzothienyl, benzofuranyl, imidazopyridinyl.

Optical isomers are understood as being the diastereoisomers and the enantiomers.

10 Among the pharmaceutically acceptable bases there may be mentioned, without implying any limitation, sodium hydroxide, potassium hydroxide, arginine, lysine, triethylamine and tert-butylamine.

One aspect of the present invention relates to the compounds of formula (IA), a particular case of the compounds of formula (I):



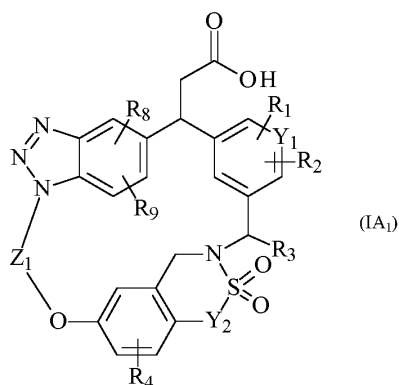
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wherein Z, Y<sub>1</sub>, Y<sub>2</sub>, R<sub>1</sub> to R<sub>9</sub> are as defined for formula (I),

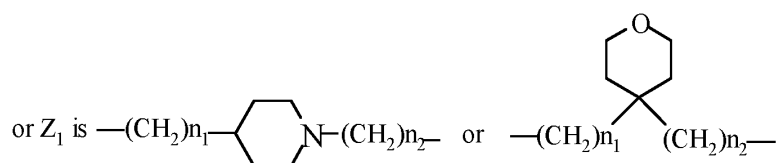
their optical isomers, and addition salts thereof with a pharmaceutically acceptable base.

Another aspect of the present invention relates to the compounds of formula (IA<sub>1</sub>), a particular  
 20 case of the compounds of formula (I) :

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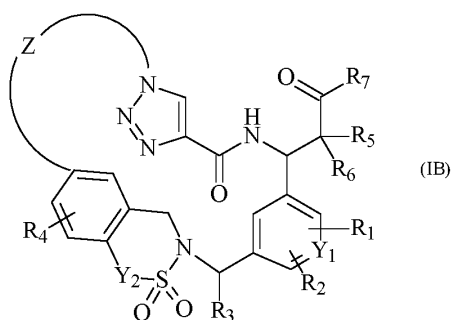


wherein R<sub>1</sub>-R<sub>4</sub>, R<sub>8</sub>-R<sub>9</sub>, Y<sub>1</sub>, Y<sub>2</sub> are as defined before, and Z<sub>1</sub> is a group selected from  
 -(CH<sub>2</sub>)<sub>n<sub>1</sub></sub>, -(CH<sub>2</sub>)<sub>n<sub>1</sub></sub>-O-(CH<sub>2</sub>)<sub>n<sub>2</sub></sub>, -(CH<sub>2</sub>)<sub>n<sub>1</sub></sub>-S-(CH<sub>2</sub>)<sub>n<sub>2</sub></sub>, -(CH<sub>2</sub>)<sub>n<sub>1</sub></sub>-NR-(CH<sub>2</sub>)<sub>n<sub>2</sub></sub>, -(CH<sub>2</sub>)<sub>n<sub>1</sub></sub>-CHR'-  
 (CH<sub>2</sub>)<sub>n<sub>2</sub></sub>, -(CH<sub>2</sub>)<sub>n<sub>1</sub></sub>-Ar<sub>1</sub>-(CH<sub>2</sub>)<sub>n<sub>2</sub></sub>, -(CH<sub>2</sub>)<sub>n<sub>1</sub></sub>-Ar<sub>1</sub>-O-(CH<sub>2</sub>)<sub>n<sub>2</sub></sub>, -(CH<sub>2</sub>)<sub>n<sub>1</sub></sub>-Ar<sub>1</sub>-S-(CH<sub>2</sub>)<sub>n<sub>2</sub></sub>, -(CH<sub>2</sub>)<sub>n<sub>1</sub></sub>-  
 5 Ar<sub>1</sub>-CHR'-(CH<sub>2</sub>)<sub>n<sub>2</sub></sub>, -Ar<sub>1</sub>-NR-(CH<sub>2</sub>)<sub>n<sub>1</sub></sub>,



their optical isomers, and addition salts thereof with a pharmaceutically acceptable base.

Another aspect of the present invention relates to the compounds of formula (IB), a particular  
 10 case of the compounds of formula (I) :

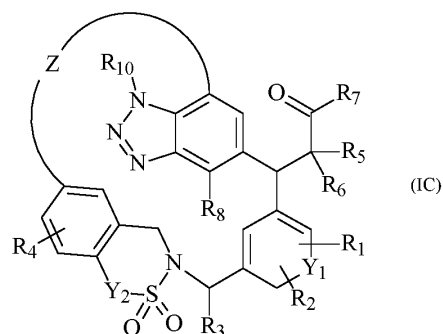


wherein Z, Y<sub>1</sub>, Y<sub>2</sub>, R<sub>1</sub> to R<sub>7</sub> are as defined before,

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their optical isomers, and addition salts thereof with a pharmaceutically acceptable base.

Another aspect of the present invention relates to the compounds of formula (IC), a particular case of the compounds of formula (I) :



5

wherein Z, Y<sub>1</sub>, Y<sub>2</sub>, R<sub>1</sub> to R<sub>8</sub> and R<sub>10</sub> are as defined before,

their optical isomers, and addition salts thereof with a pharmaceutically acceptable base.

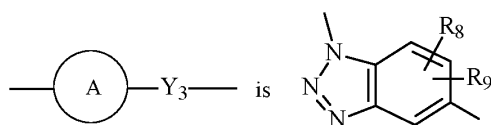
Another aspect of the present invention relates to the compounds of formula (I) wherein Z is -O-(CH<sub>2</sub>)<sub>n1</sub>-, -O-(CH<sub>2</sub>)<sub>n1</sub>-O-(CH<sub>2</sub>)<sub>n2</sub> or -O-(CH<sub>2</sub>)<sub>n1</sub>-S-(CH<sub>2</sub>)<sub>n2</sub>.

10 Another aspect of the present invention relates to the compounds of formula (I) wherein Y<sub>1</sub> is C.

Another aspect of the present invention relates to the compounds of formula (I) wherein Y<sub>2</sub> is O or NCH<sub>3</sub>.

15

Another aspect of the present invention relates to the compounds of formula (I) wherein



Another aspect of the present invention relates to the compounds of formula (I) wherein R<sub>7</sub> is

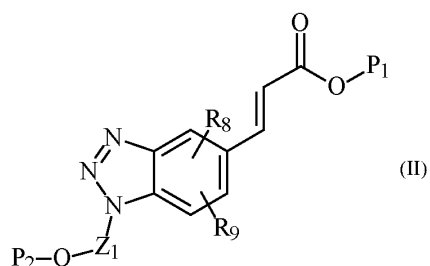
20

hydroxyl.

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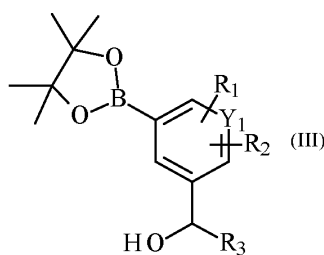
Another aspect of the present invention relates to a process for the preparation of a compound of formula (IA<sub>1</sub>), a particular case of the compounds of formula (I):

5 starting from a compound of formula (II) :



wherein  $P_1$  is a protecting group of the acid function such as alkyl, and  $P_2$  is a protecting group of the alcohol function,

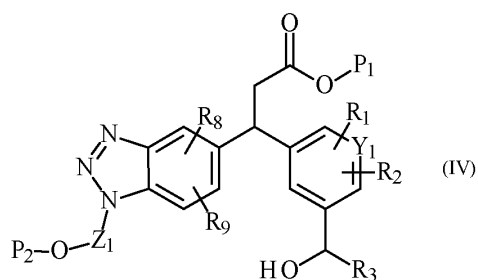
which is reacted with a compound of formula (III) :



10

wherein  $R_1$ - $R_3$  and  $Y_1$  are as defined for formula (I),

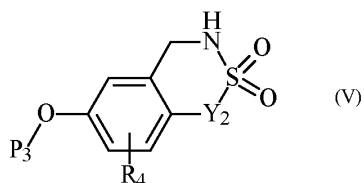
to give a compound of formula (IV) :



wherein  $R_1$ - $R_3$ ,  $R_8$ - $R_9$ ,  $Y_1$ ,  $Z_1$  and  $P_1$ - $P_2$  are as defined before,

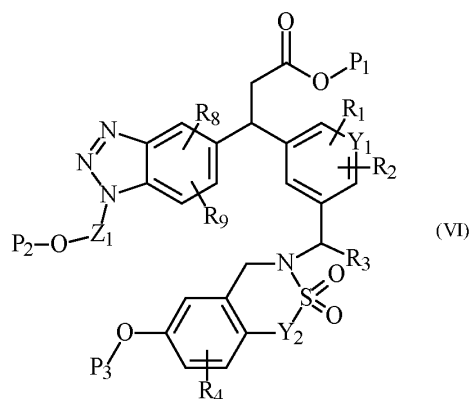
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which is reacted with a compound of formula (V) :

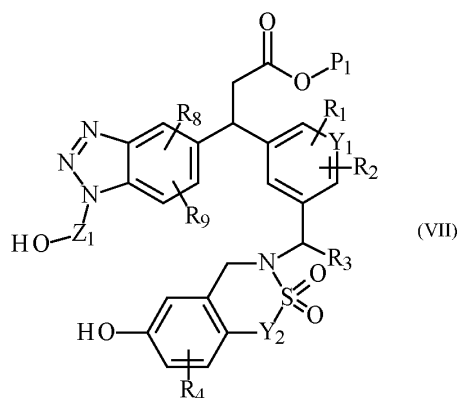


wherein  $R_4$  and  $Y_2$  are as defined for formula (I), and  $P_3$  is a protecting group of the alcohol function,

5 to give a compound of formula (VI) :



wherein  $R_1$ - $R_4$ ,  $R_8$ - $R_9$ ,  $Y_1$ ,  $Y_2$ ,  $Z_1$  and  $P_1$ - $P_3$  are as defined before,  
which is deprotected to give a compound of formula (VII) :

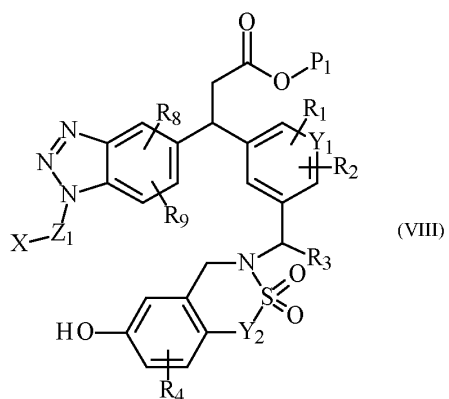


10 wherein  $R_1$ - $R_4$ ,  $R_8$ - $R_9$ ,  $Y_1$ ,  $Y_2$ ,  $Z_1$  and  $P_1$  are as defined before,



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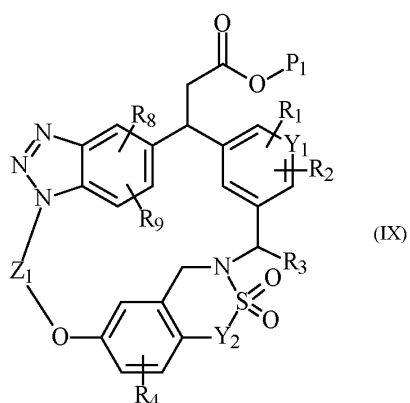
which is halogenated to give a compound of formula (VIII) :



wherein R<sub>1</sub>-R<sub>4</sub>, R<sub>8</sub>-R<sub>9</sub>, Y<sub>1</sub>, Y<sub>2</sub>, Z<sub>1</sub> and P<sub>1</sub> are as defined before, and X is a halogen atom such as Br or Cl,

5

which is reacted with a base (such as  $\text{Cs}_2\text{CO}_3$ ) to give a compound of formula (IX) :



which is deprotected by reaction of a base such as LiOH to give a compound of formula (IA<sub>1</sub>), the stereoisomers thereof are separated, if desired, using chiral separation techniques.

10

The compounds of the invention are Nrf2 activators.

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As such, they can be used in the treatment of diseases that are linked to increased oxidative stress and inflammation, impaired redox potential, impaired detoxification and deregulated metabolism, including Type I diabetes and Type II diabetes and associated complications such as diabetic cardiomyopathy, diabetic retinopathy, diabetic neuropathy, diabetic nephropathy and  
5 diabetic wound healing; Maternal diabetes; Liver diseases such as Nonalcoholic Steatohepatitis (NASH), Non-Alcoholic Fatty Liver Disease, toxin-induced liver disease (e.g., acetaminophen-induced hepatic disease), Alcoholic Liver Disease (ALD), cholestasis, Primary Sclerosing Cholangitis (PSC), viral hepatitis, cirrhosis, Primary Biliary Cirrhosis (PBC), End Stage Liver Disease, Fibrosis; Kidney diseases such as Chronic kidney disease (CKD), Acute kidney injury,  
10 Contrast-induced nephropathy, Autosomal dominant polycystic kidney disease (ADPKD), Alström and Alport syndromes, sepsis-induced acute kidney injury; kidney disease or malfunction seen during kidney transplantation, focal segmental glomerulosclerosis, IgA glomerulonephritis/nephropathy, fibrosis; Lung diseases such as pulmonary fibrosis, Idiopathic Pulmonary Fibrosis (IPF), cystic fibrosis, Acute lung injury, Lung infection, Chronic  
15 Obstructive Pulmonary Disease (COPD), Emphysema, Pulmonary Arterial Hypertension, Lung disease secondary to environmental exposures, chronic and acute asthma, acute respiratory distress syndrome; Cardiac diseases such as atherosclerosis, hypertension, heart failure, stroke, cardiomyopathy, coronary heart disease, Myocardial Ischemia; Neuronal damage, Traumatic brain injury, Depression, Epilepsy, Hepatic Encephalopathy, Huntington's disease, Parkinson's  
20 disease, Alzheimer's disease, autism, Friedreich's ataxia, Amyotrophic Lateral Sclerosis (ALS), Multiple Sclerosis (MS), Stroke, Cerebral infarction, Encephalopathy, neuronal damage/injury, Spinal cord injury; Inflammatory diseases such as inflammatory bowel disease, Ulcerative Colitis, Crohn's Disease, Pancreatitis, Arthritis, lupus nephritis; Eye diseases such as Age-related macular degeneration (AMD), Ocular Neurodegenerative Diseases, Age-related macular  
25 degeneration, cataracts, glaucoma, eye injury, Fuchs Endothelial Corneal Dystrophy (FECD), uveitis, Optic neuropathy/Ocular Neurodegenerative Diseases; Colon cancer; Autoimmune diseases; Psoriasis, dermatitis/topical effects of radiation, immunosuppression due to radiation exposure, Preeclampsia, High altitude sickness; Wound healing; Metabolic syndrome; Mitochondrial myopathies; Malaria; Ferroptosis/iron overload; Allergic contact dermatitis;  
30 Alcohol dependence; Amyloidosis; Anemia; Anxiety disorder; Asperger syndrome; Eczema;

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Brain edema; Brain ischemia; Cerebrovascular disorder; Chronic fatigue syndrome; Cognitive decline; Dermatitis/radiation-induced dermatitis; Duchenne muscular dystrophy; Edema; Encephalitis; Male/female fertility; Fracture healing; Gastroesophageal reflux disease; Hearing loss; influenza infections; Intestinal barrier dysfunction; Osteoarthritis; Osteoporosis;  
5 Radiation-induced injury; Reflux-Induced Esophagitis; Reperfusion injury (brain, heart, kidney, liver, retina); Schizophrenia; Seizures; Sjogren syndrome; Sickle cell disease; Skin ulcer; Vascular endothelial dysfunction; Blood-brain barrier dysfunction; Down syndrome.

The compounds according to the invention are especially useful for the treatment of Type II  
10 diabetes and NASH.

The present invention also relates to pharmaceutical compositions comprising a compound of formula (I) in combination with one or more inert, non-toxic, pharmaceutically acceptable excipients or carriers.  
15

The useful dosage varies according to the age and weight of the patient, the administration route, the nature and severity of the disorder and any associated treatments, and ranges from 0.5 mg to 1000 mg per day in one or more administrations.

20 Among the pharmaceutical compositions according to the invention there may be mentioned more especially those that are suitable for oral, parenteral (intravenous, intramuscular or subcutaneous), per- or trans-cutaneous, nasal, rectal, perlingual, ocular or respiratory administration, and especially tablets or dragées, sublingual tablets, gelatin capsules, capsules, suppositories, creams, ointments, dermal gels, injectable or drinkable preparations, aerosols, and  
25 eye or nasal drops.

According to one aspect of the present invention, the pharmaceutical composition is a tablet for oral administration.

In addition to the compound of formula (I), the tablets according to the invention comprise one  
30 or more excipients or carriers, such as diluents, lubricants, binders, disintegrators, absorbents,

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colourants and sweeteners.

There may be mentioned as examples of excipients or carriers:

- ♦ *for the diluents*: lactose, dextrose, sucrose, mannitol, sorbitol, cellulose, glycerol,
- ♦ *for the lubricants*: silica, talc, stearic acid and its magnesium and calcium salts, polyethylene glycol,
- ♦ *for the binders*: aluminium and magnesium silicate, starch, gelatin, tragacanth, methylcellulose, sodium carboxymethylcellulose and polyvinylpyrrolidone,
- ♦ *for the disintegrators*: agar, alginic acid and its sodium salt, effervescent mixtures.

- 10 The percentage of active ingredient of formula (I) in the tablet is preferably between 5% and 50% by weight.

According to one aspect of the present invention, the compound of formula (I) according to the present invention is administered in association with one or more additional active ingredients. The administration in association may be in the form of a simultaneous or successive co-administration of two or more separate pharmaceutical compositions each containing one of the active ingredients (free association), or in the form of the administration of a fixed association of the two or more active ingredients in the same pharmaceutical composition.

More specifically, the compounds of formula (I) and pharmaceutically acceptable salts thereof may be used in combination with one or more other active ingredients useful in the prevention or treatment of diabetes or NASH, including biguanides, sulfonylureas, DPP 4 inhibitors, SGLT2 inhibitors, GLP1 agonists, dual GLP1-GCG or GLP1-GIP agonists, FXR agonists, PPAR modulators, Thyroid hormone receptor agonists, FGF21 agonists, FGF19 agonists, DGAT2 inhibitors, ACC inhibitors or FAS inhibitors.

### **ABBREVIATIONS**

- 20 **abs.:** absolute

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- AcOH:** acetic acid
- aq. :** aqueous
- A<sup>ta</sup>phos.PdCl<sub>2</sub>:** bis(di-*tert*-butyl(4-dimethylaminophenyl) phosphine) dichloropalladium(II)
- Cs<sub>2</sub>CO<sub>3</sub>:** cesium carbonate
- 5    **°C:** degree Celsius
- DCM:** dichloromethane
- DDQ:** 2,3-dichloro-5,6-dicyano-1,4-benzoquinone
- dia:** diastereomer
- DIAD:** diisopropyl azodicarboxylate
- 10    **Dioxane:** 1,4-dioxane
- DIPEA:** diisopropylethyl amine, *N*-ethyl-*N*-(propan-2-yl)propan-2-amine
- DMEM :** Dulbecco's Modified Eagle Medium
- DMF:** N,N-dimethylformamide
- DMSO:** dimethyl sulfoxide
- 15    **E1:** first-eluted enantiomer
- E2:** second-eluted enantiomer
- Et<sub>2</sub>O :** diethyl ether
- EtOAc:** ethyl acetate
- EtOH:** ethanol
- 20    **FBS :** Fetal Bovine Serum
- g :** gram(s)
- h:** hour(s)
- HCl:** hydrochloric acid
- HCOOH:** formic acid
- 25    **HEC:** HydroxyEthyl Cellulose
- H<sub>2</sub>SO<sub>4</sub>:** sulfuric acid
- HPLC:** high performance liquid chromatography
- HRMS:** high-resolution mass spectrometry
- IPA:** propan-2-ol
- 30    **K<sub>2</sub>CO<sub>3</sub>:** potassium carbonate

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- LC:** liquid chromatography  
**LC-MS:** liquid chromatography-mass spectroscopy  
**LiOH:** lithium hydroxide  
**M:** molar
- 5    **MeOH:** methanol  
     **MeCN:** acetonitrile  
     **mg:** milligram(s)  
     **MgSO<sub>4</sub>:** magnesium sulfate  
     **MHz:** megahertz
- 10   **min:** minute(s)  
     **mL:** milliliter(s)  
     **mmol:** millimole(s)  
     **MS:** mass spectroscopy  
     **MTBE:** methyl-*tert*-butylether
- 15   **N<sub>2</sub>:** nitrogen gas  
     **NaCl:** sodium chloride  
     **NaH :** sodium hydride  
     **NaOH :** sodium hydroxide  
     **NaHCO<sub>3</sub>:** sodium hydrogen carbonate
- 20   **Na<sub>2</sub>SO<sub>4</sub>:** sodium sulfate  
     **NBS:** N-bromosuccinimide  
     **NH<sub>4</sub>HCO<sub>3</sub>:** ammonium hydrogen carbonate  
     **NH<sub>4</sub>Cl:** ammonium chloride  
     **NMR:** nuclear magnetic resonance
- 25   **NMP:** N-methyl pyrrolidone  
     **Pd/C:** palladium on activated carbon  
     **Pd<sub>2</sub>(dba)<sub>3</sub>:** tris(dibenzylideneacetone)dipalladium(0)  
     **PPh<sub>3</sub>:** triphenylphosphine  
     **quant.:** quantitative yield
- 30   **rac:** racemic

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**RT:** room temperature

**sat.:** saturated

**tBuXPhos:** 2-di-*tert*-butylphosphino-2',4',6'-triisopropylbiphenyl

**TEA:** triethylamine

5 **TFA:** trifluoroacetic acid

**THF:** tetrahydrofuran

**wt%:** weight percent

### General information

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IUPAC chemical names were generated using ACD/Labs 2018 2.2 (File version C60H41, Build 106041, 07 Dec 2018)

All reagents obtained from commercial sources were used without further purification.

15 Anhydrous solvents were obtained from commercial sources and used without further drying.

Normal phase silica gel (flash) chromatography was performed on ISCO CombiFlash Rf 200i with pre-packed silica-gel cartridges (RediSep®Rf Gold High Performance).

20 Microwave heating was performed in an Anton Parr MonoWave or CEM Discover® instrument.

Reversed-phase (preparative) HPLC purifications were performed on a HANBON NP7000 Liquid Chromatography system with a Gemini-NX® 5µM C18, 250 mm × 50 mm i.d. column running at a flow rate of 99.9 mL min<sup>-1</sup> with UV diode array detection (210–400 nm) using pure  
25 water, or 5 mM aq. NH<sub>4</sub>HCO<sub>3</sub> solution, or 5 mM aq. HCOOH solution, or 5 mM aq. TFA solution and MeCN as eluents unless specified otherwise.

Analytical LC-MS: The compounds of the present invention were characterized by high performance liquid chromatography-mass spectroscopy (HPLC-MS) on Agilent HP1200 with  
30 Agilent 6140 quadrupole LC/MS, operating in positive or negative ion electrospray ionisation

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mode. Molecular weight scan range is 100 to 1350. Parallel UV detection was done at 210 nm and 254 nm. Samples were supplied as a 1 mM solution in ACN, or in THF-water (1:1) with 5  $\mu$ L loop injection. LC-MS analyses were performed on two instruments, one of which was operated with basic, and the other with acidic eluents.

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Basic LC-MS: Gemini-NX, 3  $\mu$ m, C18, 50 mm  $\times$  3.00 mm i.d. column at 23  $^{\circ}$ C, at a flow rate of 1 mL min<sup>-1</sup> using 5 mM NH<sub>4</sub>HCO<sub>3</sub> (Solvent A) and acetonitrile (Solvent B) with a gradient starting from 100 % Solvent A and finishing at 100 % Solvent B over various/certain duration of time.

10

Acidic LCMS: ZORBAX Eclipse XDB-C18, 1.8  $\mu$ m, 50 mm  $\times$  4.6 mm i.d. column at 40  $^{\circ}$ C, at a flow rate of 1 mL min<sup>-1</sup> using 0.02 % v/v aq. HCOOH (Solvent A) and 0.02 % v/v HCOOH in MeCN (Solvent B) with a gradient starting from 100% Solvent A and finishing at 100 % Solvent B over various/certain duration of time.

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<sup>1</sup>H-NMR measurements were performed on Bruker Avance III 500 MHz spectrometer and Bruker Avance III 400 MHz spectrometer, using DMSO-d<sub>6</sub> (hexadeutero-dimethylsulfoxide) or CDCl<sub>3</sub> (deuteriochloroform) as solvent. <sup>1</sup>H-NMR data is in the form of delta values, given in part per million (ppm), using the residual peak of the solvent (2.50 ppm for DMSO-d<sub>6</sub> and 7.26 ppm for CDCl<sub>3</sub>) as internal standard. Splitting patterns are designated as: s (singlet), 2s (2xsinglet), d (doublet), 2d (2xdoublet), t (triplet), 2t (2xtriplet), q (quartet), 2q (2xquartet), quint (quintet), sept (septet), m (multiplet), 2m (2xmultiplet), brs (broad singlet), brd (broad doublet), brt (broad triplet), brq (broad quartet), brm (broad multiplet), vbrs (very broad singlet), dd (doublet of doublets), td (triplet of doublets), dt (doublet of triplets), dq (doublet of quartets), ddd (doublet of doublet of doublets), dm (doublet of multiplets), tm (triplet of multiplets), qm (quartet of multiplets).

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HRMS were determined on a Shimadzu IT-TOF, ion source temperature 200  $^{\circ}$ C, ESI +/-, ionization voltage: (+-)4.5 kV. Mass resolution min. 10000.

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The final products or final intermediates were separated to pure enantiomers / diastereomers using chiral supercritical fluid chromatography (SFC) in milligram scale using SFC-PICLAB-PREP 200 equipment (Pic Solution) by the following methods:

- 5       • The mobile phase is carbon dioxide as a supercritical fluid or a mixture fluid (by adding a protic solvent, for example: isocratic 35-45% IPA or EtOH / supercritical CO<sub>2</sub>)
- The column was chosen according to the chromatography profile, for example:
  - Whelk 01 RR 30 x 250mm x 5µm (particle size) or
  - 10       LUX (Phenomenex) 30 mm x 150mm x 5µm (particle size) or
  - Chiralpak IG 30 x 250mm x 5µm (particle size)
- Temperature: 40°C
- Detection: at 230 nm
- Flowrate: 120-150 mL/min.

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The examples which follow illustrate the present invention.

### **GENERAL PROCEDURE 1**

#### **20   General procedure 1 STEP 1**

To a solution of 1-fluoro-3-methyl-2-nitro-benzene (1 eq., 64.5 mmol) in MeCN (2 mL/mmol, 101.3 g, 128.92 mL) the amino alcohol (3 eq., 193.5 mmol) was added at RT. The reaction mixture was heated to 70 °C and stirred overnight. After completion of the reaction, the solvent  
25   was evaporated under reduced pressure. The residue was partitioned between 250 mL of water and 200 mL of EtOAc. The separated organic layer was washed with further 150 mL of brine. The combined aq. layers were washed with 100 mL EtOAc. The combined organic layers were dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>, filtered, concentrated to dryness to give the crude product, which was purified by normal phase silica gel chromatography using heptane-EtOAc (for example  
30   100:0 to 75:25) as an eluent to give the title compound.

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**General procedure 1 STEP 2**

To a solution of the General procedure 1 STEP 1 product (1 eq., 834 mmol) in AcOH (1.2 mL/mmol, 42 g, 40 mL) NBS (1 eq., 6 g, 34 mmol) was added at RT. The reaction mixture was heated to 110 °C and stirred for 2 h. After completion of the reaction, the mixture was cooled to RT and quenched with 200 ml of ice cold water. The pH was set to 14 by NaOH solution. The mixture was stirred at RT for 10 min. The mixture was extracted with 3x150 ml DCM. The combined organic layers were washed with brine. The organic phase was dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>, filtered, concentrated to dryness to give the title compound, which was used in the next step without further purification or purified with reversed-phase chromatography using water-MeCN as an eluent.

**General procedure 1 STEP 3**

To a solution of the General procedure 1 STEP 2 product (1 eq., 35.1 mmol) or an appropriate aryl nitro compound in EtOH (25 mL/mmol, 692 g, 877 mL) and water (3 mL/mmol, 105 g, 105 mL), iron powder (15 eq., 29.4 g, 526 mmol) and NH<sub>4</sub>Cl (5 eq., 9.38 g, 175 mmol) were added at RT. The reaction mixture was heated to 50 °C and stirred for 2 h. After completion of the reaction, the mixture was filtered through a pad of Celite, then washed with 2x100 ml of EtOH. The solvent was evaporated under reduced pressure, the evaporation residue was dissolved in 100 ml of DCM. The solution was dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>, filtered, concentrated to dryness to give the title compound, which was used in the next step without further purification.

**General procedure 1 STEP 4**

To a solution of General procedure 1 STEP 3 product (1 eq., 32 mmol) in AcOH (0.3 mL/mmol, 10 g, 9.6 mL) and water (3 mL/mmol, 96 g, 96 mL) H<sub>2</sub>SO<sub>4</sub> (0.3 mL/mmol, 18 g, 9.6 mL) was added at 0°C. Sodium nitrite (1.5 eq., 3.3 g, 48 mmol) was added by portions and the reaction

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mixture was stirred at 0 °C for 10 min. The resulted dark heterogeneous mixture was allowed to warm to RT and stirred for further 30 min. After completion of the reaction, the mixture was quenched with 300 mL water and the pH was set to ~12 using concentrated NaOH solution. The mixture was extracted with 3x70 ml DCM. The organic layer was washed with 150 mL of brine.

- 5 The organic layer was dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>, filtered, concentrated to dryness to give a black oil, which was purified by normal phase silica gel chromatography using DCM-EtOAc (100:0 to 70:30) eluents to give the title compound.

#### General procedure 1 STEP 5

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To a solution of General procedure 1 STEP 4 product (1 eq., 22 mmol) in THF (10 mL/mmol, 200 g, 220 mL), water (5 mL/mmol, 110 g, 110 mL) and MeOH (2.5 mL/mmol, 44 g, 55 mL) LiOH (3 eq., 1.6 g, 66 mmol) was added at RT and the mixture was stirred for further 30 min. After completion of the reaction, the mixture was quenched with 400 mL water and 50 mL of 2 M aq. HCl solution. The mixture was extracted with 3x20 ml EtOAc. The organic layer was washed with brine and dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>, filtered, concentrated to dryness to give an oil, which was purified by normal phase silica gel chromatography using DCM-EtOH (100:0 to 80:20) as an eluent to give the title compound.

#### 20 General procedure 1 STEP 6

- To a solution of General procedure 1 STEP 5 product (1 eq., 10 mmol) in THF (7 mL/mmol, 63 g, 70 mL) NaH (1.2 eq., 480 mg, 12 mmol, 60 wt% in mineral oil) was added at 0°C. The mixture was allowed to warm to RT and was stirred at this temperature for 30 min. The reaction mixture was cooled to 0°C, 4-methoxy-benzylchloride (1.2 eq., 1.9 g, 12 mmol) was added and the mixture was stirred overnight at RT. After completion of the reaction, the mixture was quenched with 100 mL water and extracted with 3x100 ml EtOAc. The combined organic layers were washed with brine. The organic layer was dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>, filtered, concentrated to dryness to give an orange oil, which was purified by normal phase silica gel chromatography using heptane-EtOAc (100:0 to 75:25) as an eluent to give the title compound.
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**General procedure 1 STEP 7**

To a solution of General procedure 1 STEP 6 product (1 eq., 7.1 mmol) in DMF (7 mL/mmol, 5 47.4 g, 50 mL) ethyl prop-2-enoate (2 eq., 1.44 g, 1.56 mL, 14.2 mmol), DIPEA (3 eq., 2.78 g, 3.75 mL, 21.5 mmol), tris-*o*-tolylphosphine (0.2 eq., 0.44 g, 1.4 mmol) and palladium diacetate (0.1 eq. 0.161 g, 0.71 mmol) were added at RT. The mixture was flushed twice with argon and heated in a closed Schlenk tube overnight at 100 °C. After completion of the reaction, the solvent was evaporated to dryness under reduced pressure to afford a black oil, which was purified by 10 normal phase silica gel chromatography using heptane-EtOAc (100:0 to 75:25) as an eluent to give the title compound.

**GENERAL PROCEDURE 2**15 **General procedure 2 STEP 1**

To a solution of 1-fluoro-3-methyl-2-nitro-benzene (1 eq., 1.93 mmol) in MeCN (2 mL/mmol, 101.3 g, 128.92 mL), the O-benzyl-amino alcohol (1.2 eq., 2.32 mmol) was added followed by addition of Cs<sub>2</sub>CO<sub>3</sub> (2 eq., 1.26 g, 3.87 mmol) or TEA (2 eq., 3.87 mmol) at RT. The reaction 20 mixture was heated to 70 °C and stirred at this temperature overnight. After completion of the reaction, the mixture was filtered, the mother liquor was evaporated under reduced pressure. The crude product was purified by reversed-phase chromatography using water-MeCN gradient elution (95:5 to 0:100) to give the title compound.

25 **General procedure 2 STEP 2**

To a solution of the General procedure 2 STEP 1 product (1 eq., 22 mmol) in AcOH (26 mL) NBS (1.2 eq., 4.6 g, 26 mmol) was added at RT. The reaction mixture was heated to 110 °C and stirred for 1.5 h. After completion of the reaction, the mixture was cooled to RT, quenched with 30 200 mL of ice cold water. The pH was adjusted to 14 using NaOH solution. The mixture was

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stirred at RT for 10 min. The mixture was extracted with 3x150 ml DCM. The combined organic layers were washed with brine. The organic phase was dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>, filtered, concentrated to dryness to give the title compound, which was purified by reversed-phase chromatography using water-MeCN gradient elution (95:5 to 0:100) to give the title compound.

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**General procedure 2 STEP 3**

To a solution of the General procedure 2 STEP 2 product (1 eq., 17 mmol) in EtOH (430 mL) (or IPA) and water (50 mL), iron powder (15 eq., 14 g, 260 mmol) and NH<sub>4</sub>Cl (5.5 eq., 5 g, 93.5 mmol) were added at RT. The reaction mixture was heated to 50 °C and stirred at this temperature overnight. After completion of the reaction, the mixture was filtered through a pad of Celite and washed with 2x100 ml of EtOH. The mother liquor was concentrated under reduced pressure. The crude product was purified by reversed-phase chromatography using water-MeCN gradient elution (95:5 to 0:100) to give the title compound.

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**General procedure 2 STEP 4**

To a solution of General procedure 2 STEP 3 product (1 eq., 13 mmol) in AcOH (30 mL) and water (30 mL), H<sub>2</sub>SO<sub>4</sub> (8.9 g, 4.6 mL, 90 mmol) was added at 0°C. Sodium nitrite (1.5 eq., 3.3 g, 48 mmol) was added in small portions and the reaction mixture was stirred at 0°C for 10 min. The resulted dark heterogeneous mixture was allowed to warm to RT and was stirred at this temperature for further 30 min. After completion of the reaction, the mixture was quenched with 300 mL water and the pH was set to ~12 using 2 M aq. NaOH solution. The mixture was extracted with 3x70 ml DCM. The combined organic layers were washed with 150 mL of brine. The organic layer was dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>, filtered, concentrated to dryness to give the crude product, which was purified by normal phase silica gel chromatography using DCM-EtOAc (100:0 to 95:5) as an eluent to give the title compound.

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**General procedure 2 STEP 5**

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To a solution of General procedure 2 STEP 4 product (1 eq., 2.91 mmol) in DMF (20 mL) ethyl prop-2-enoate (2.2 eq., 642 g, 0.699 mL, 6.41 mmol), DIPEA (3 eq., 1.13 g, 1.52 mL, 8.74 mmol), tris-*o*-tolylphosphine (0.2 eq., 0.177 g, 0.583 mmol) and palladium acetate (0.1 eq. 0.65 g, 0.291 mmol) were added at RT. The mixture was flushed twice with argon and heated in a closed Schlenk tube overnight at 100 °C. After completion of the reaction the solvent was evaporated to dryness under reduced pressure. The crude product was purified by normal phase silica gel chromatography using DCM-EtOH (100:0 to 95:5) as an eluent to give the title compound.

### 10 **GENERAL PROCEDURE 3**

The aryl-bromide derivative (1 eq., 10 mmol) was introduced into a round bottom flask and dissolved in dioxane (5 mL/ mmol, 50 mL). 4,4,5,5-Tetramethyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,3,2-dioxaborolane (1.1 eq., 2.79 g, 11 mmol) and dry potassium acetate (3.5 eq., 3.43 g, 35 mmol) were added at RT. The mixture was flushed with argon or nitrogen. Finally [1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium(II) catalyst (0.02 eq., 146 mg, 0.2 mmol) was added and the mixture was flushed again with argon or nitrogen before heating at 75°C overnight under inert atmosphere. After completion of the reaction, the mixture was filtered through a pad of Celite and the mother liquor was evaporated to dryness under reduced pressure. The crude product was purified by normal phase silica gel chromatography using DCM-EtOAc (100:0 to 90:10) as an eluent, or by reversed-phase chromatography using water-MeCN (95:5 to 0:100) as an eluent to give the title compound.

### 25 **GENERAL PROCEDURE 4**

#### **General procedure 4 STEP 1**

Paraformaldehyde (3 eq., 12.8 mmol), magnesium dichloride (2 eq., 0.812 mg, 8.5 mmol) and TEA (2 eq., 1.18 mL, 8.5 mmol) were introduced into a round bottom flask. The mixture was

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dissolved in THF (20 mL) and stirred for 30 min at RT. The substituted phenol (1 eq., 4.3 mmol) was added and the mixture was stirred at reflux temperature overnight. After completion of the reaction the solvent was evaporated to dryness under reduced pressure. The residue was diluted with 50 mL EtOAc, washed with 50 mL 1 M HCl solution, then with 50 mL brine. The organic  
5 layer was dried over anhydrous MgSO<sub>4</sub>, filtered, concentrated to obtain the crude product, which was purified by normal phase silica gel chromatography using heptane-EtOAc as an eluent to give the title compound.

#### General procedure 4 STEP 2

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Chlorosulfonyl isocyanate (4 eq., 13 g, 8.1 mL, 93 mmol) was introduced into a round bottom flask at 0°C. HCOOH (4 eq., 3.5 mL, 93 mmol) was added dropwise over a period of 40 min at 0°C. The mixture was allowed to warm to RT over a period of 30 min and the stirring at RT was continued for additional 1h. The mixture was cooled to 0°C and General procedure 4 STEP 1  
15 product (1 eq., 23 mmol) dissolved in NMP (3.5 mL/mmol, 81 mL) was added dropwise over a period of 10 min. The mixture was allowed to warm to RT and stirred at this temperature overnight. After completion of the reaction, the mixture was quenched with 500 mL aq. sat. NH<sub>4</sub>Cl solution. The mixture was extracted with 2x200 mL EtOAc, the combined organic layers were dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>, filtered, concentrated to dryness to give the crude product,  
20 which was purified by normal phase silica gel chromatography using heptane-EtOAc (100:0 to 50:50) as an eluent to give the title compound.

#### General procedure 4 STEP 3

25 To a cooled solution of General procedure 4 STEP 2 product (1 eq., 22.4 mmol) in MeOH (8 mL/mmol, 179 mL) at -5°C sodium borohydride (1.2 eq., 1.02 g, 26.9 mmol) was added slowly over a period of 20 min. The mixture was stirred for 1 h at -5°C. After completion of the reaction, the mixture was allowed to warm to RT and concentrated to dryness to give the crude product, which was purified by normal phase silica gel chromatography using DCM-EtOH (100:0 to  
30 99:1) as an eluent, or by reversed-phase chromatography using water-MeCN gradient elution

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(95:5 to 0:100) to give the title compound.

### **GENERAL PROCEDURE 5**

#### **5 General procedure 5 STEP 1**

To a stirred solution of the 6-bromo-3,4-dihydro-1,2λ<sup>6</sup>,3-benzoxathiazine 2,2-dioxide derivative (1 eq., 17 mmol) in DCM (92 mL), TEA (1.1 eq., 2.5 mL, 18 mmol), N,N-dimethylpyridin-4-amine (0.1 eq., 0.2 g, 1.7 mmol) and di-tert-butyl-dicarbonate (1.1 eq., 4 g, 18 mmol) were added at RT. The mixture was stirred overnight at RT. After completion of the reaction the mixture was extracted with 3x50 ml 10 wt% aq. citric acid solution, then with 50 ml water. The organic layer was dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>, filtered, concentrated to dryness to give the title compound, which was used in a next step without further purification.

#### **15 General procedure 5 STEP 2**

General procedure 5 STEP 1 product (1 eq., 16 mmol) was introduced into a round bottom flask and dissolved in dioxane (7.5 mL/mmol, 120 mL). 4,4,5,5-Tetramethyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,3,2-dioxaborolane (1.1 eq., 4.6 g, 18 mmol) and dry potassium acetate (3.5 eq., 5.6 g, 57 mmol) were added to the mixture at RT. The mixture was flushed with argon or nitrogen. Finally [1,1'-bis(diphenylphosphino) ferrocene]dichloropalladium(II) catalyst (0.02 eq., 160 mg, 0.33 mmol) was added and the mixture was flushed again with argon or nitrogen. After heating at 75°C overnight under inert atmosphere. The mixture was filtered through a Celite pad, and the mother liquor was concentrated to dryness under reduced pressure. The crude product was purified by normal phase silica gel chromatography using heptane-EtOAc (100:0 to 80:20) as an eluent to give the title compound.

#### **General procedure 5 STEP 3**

30 To a stirred solution of General procedure 5 STEP 2 product (1 eq., 11.5 mmol) in EtOH (15



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mL/mmol, 73 mL) and water (7.5 mL/mmol, 37 mL), *m*-chloro-perbenzoic acid (1 eq., 2.84 g, 11.5 mmol) was added at RT in portions. The mixture was stirred overnight at RT. After completion of the reaction the mixture was quenched with 100 mL sat. aq. NaHCO<sub>3</sub> solution. The mixture was extracted with 3x50 ml of EtOAc. The combined organic layers were washed  
5 with 50 mL sat. aq. NaHCO<sub>3</sub> solution, then with 50 mL water. The organic layer was dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>, filtered, concentrated to dryness to give the crude product, which was purified by normal phase silica gel chromatography using heptane-EtOAc (100:0 to 50:50) as an eluent to give the title compound.

#### 10 **General procedure 5 STEP 4**

To a solution of General procedure 5 STEP 3 product (1 eq., 9.2 mmol) in MeCN (58 mL), Cs<sub>2</sub>CO<sub>3</sub> (2.4 eq., 7.2 g, 22 mmol) and benzylbromide (2.2 eq., 3.4 g, 2.4 mL, 20 mmol) were added and the mixture was stirred overnight at RT. After completion of the reaction the solvent  
15 was evaporated under reduced pressure, then diluted with 40 ml EtOAc. The mixture was washed with 40 mL brine, then with 40 mL water. The organic layer was dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>, filtered, concentrated to dryness to give the crude product, which was used in the next step without further purification.

#### 20 **General procedure 5 STEP 5**

To a solution of General procedure 5 STEP 4 product (1 eq., 9.2 mmol) in DCM (75 mL), TFA (8 eq., 8.4 g, 5.66 mL, 74 mmol) was added dropwise and the mixture was stirred overnight at RT. The pH of the mixture was set to 9 using sat. aq. NaHCO<sub>3</sub> solution. The layers were  
25 separated, the organic layer was extracted with 30 mL brine, then 30 mL water. The organic layer was dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>, filtered, concentrated to dryness to give the crude product, which was purified by normal phase silica gel chromatography using heptane-EtOAc (100:0 to 70:30) as an eluent to afford the title compound.

#### 30 **GENERAL PROCEDURE 6**

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To a stirred solution of the ethyl aryl(prop-2-enoate) derivative or ethyl heteroaryl(prop-2-enoate) derivative (1 eq., 4.6 mmol) in dioxane (5-8 mL/mmol, 23 mL) and water (1-2.7 mL/mmol, 4.6 mL), the [3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aryl derivative (1.5-2 eq., 6.9 mmol) and TEA (1.5 eq., 0.96 mL, 6.9 mmol) were added. The suspension was flushed and degassed with argon or nitrogen. Finally chloro(1,5-cyclooctadiene)rhodium(I) dimer catalyst (0.05 eq., 56 mg, 0.23 mmol) was added and the mixture was heated at 80°C for 4-16 h under inert atmosphere. After completion of the reaction the mixture was diluted with 100 mL water, the layers were separated, the aq. layer was extracted with 2x50 mL EtOAc. The combined organic layers were washed with 50 mL brine, before drying over anhydrous Na<sub>2</sub>SO<sub>4</sub>. Filtration and concentration to dryness afforded the crude product, which was purified by normal phase silica gel chromatography using heptane-EtOAc (100:0 to 50:50) as an eluent, or by reversed-phase chromatography using water-MeCN gradient elution (95:5 to 0:100) to give the title compound.

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**GENERAL PROCEDURE 7**

To a stirred solution of the hydroxymethylphenyl derivative (1 eq., 1.6 mmol) in THF (22 mL/mmol, 35 mL), the substituted benzoxathiazine 2,2-dioxide, or 1,3-benzothiadiazine 2,2-dioxide derivative (1-2.5 eq., 2.4 mmol) and PPh<sub>3</sub> (2.2 eq., 0.93 g, 3.5 mmol) were added. The reaction mixture was cooled to 15°C and DIAD (2 eq., 0.63 mL, 3.2 mmol) was added dropwise over a period of 5 min. The mixture was allowed to warm to RT and was stirred at this temperature overnight. After completion of the reaction the mixture was concentrated to dryness and purified by normal phase silica gel chromatography using DCM-EtOAc (100:0 to 80:20) eluent, or by reversed-phase chromatography using water-MeCN gradient elution (95:5 to 0:100) to give the title compound.

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**GENERAL PROCEDURE 8**

A stainless steel hydrogenation autoclave was charged with the ethyl 3-[3-[(6-benzyloxy-2,2-

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dioxo-4H-1,2λ<sup>6</sup>,3-benzoxathiazin-3-yl)methyl]phenyl]-3-(4-methyl-1H-benzotriazol-5-yl)propanoate or ethyl 3-[3-[(6-benzyloxy-2,2-dioxo-1,4-dihydro-2,1,3-benzothiadiazin-3-yl)methyl]phenyl]-3-(4-methyl-1H-benzotriazol-5-yl)propanoate (1 eq., 0.883 mmol), Pd/C catalyst (0.1 eq., 0.0883 mmol), dioxane (3 mL), MeOH or EtOH (10 mL) and DCM (4 mL) and the autoclave was sealed, inertised, and filled with hydrogen (1-8 bar). After stirring at RT for 10-40 h, the reaction mixture was filtered through a Celite pad and the volatiles of the filtrate were evaporated to give the title compound. The crude product was purified by normal phase silica gel chromatography or by reversed-phase chromatography using water-MeCN gradient elution (95:5 to 0:100) to give the title compound.

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#### **GENERAL PROCEDURE 9**

To a stirred solution of the N-hydroxyalkyl ethyl 3-[3-[(6-hydroxy-2,2-dioxo-4H-1,2λ<sup>6</sup>,3-benzoxathiazin-3-yl)methyl]phenyl]-3-(4-methyl-1H-benzotriazol-5-yl)propanoate or N-hydroxyalkyl ethyl 3-[3-[(6-hydroxy-2,2-dioxo-1,4-dihydro-2,1,3-benzothiadiazin-3-yl)methyl]phenyl]-3-(4-methyl-1H-benzotriazol-5-yl)propanoate (1 eq., 0.122 mmol) in DCM (1 mL), carbon-tetrabromide (7 eq., 69 mg, 0.2074 mmol) and PPh<sub>3</sub> (1.7 eq., 54.4 mg, 0.2074 mmol) were added. After stirring at RT for 5-20 h, the reaction mixture was concentrated under reduced pressure, and the crude product was purified by normal phase silica gel chromatography using hexane-EtOAc gradient elution to give the title compound.

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#### **GENERAL PROCEDURE 10**

The N-hydroxyalkyl ethyl 3-[3-[(6-hydroxy-2,2-dioxo-4H-1,2λ<sup>6</sup>,3-benzoxathiazin-3-yl)methyl]phenyl]-3-(4-methyl-1H-benzotriazol-5-yl)propanoate or N-hydroxyalkyl ethyl 3-[3-[(6-hydroxy-2,2-dioxo-1,4-dihydro-2,1,3-benzothiadiazin-3-yl)methyl]phenyl]-3-(4-methyl-1H-benzotriazol-5-yl)propanoate (1 eq., 88.7 mmol) was dissolved in DCM (355 mL) under N<sub>2</sub> atmosphere. The solution was cooled to 0°C and thionyl chloride (1.2-4 eq., 12.7 g, 7.77 mL, 106.5 mmol) was added dropwise under N<sub>2</sub> atmosphere. After stirring at 40°C for 4h, the reaction mixture was cooled to 0°C. Water (155 mL) and aq. sat. NaHCO<sub>3</sub> solution (155 mL)

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were added slowly. and the layers were separated. The organic layer was washed with water, dried over MgSO<sub>4</sub>, and the solvents were removed under reduced pressure. The crude product was used without further purification, or was purified if needed by normal phase silica gel chromatography using DCM-MeOH or hexane-EtOAc gradient elution to give the title compound.

### **GENERAL PROCEDURE 11**

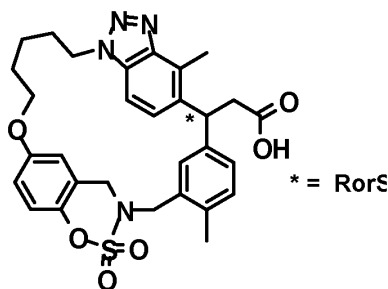
To the stirred solution of the chloro or bromoalkyl ethyl 3-[3-[(6-hydroxy-2,2-dioxo-4H-1,2λ<sup>6</sup>,3-benzoxathiazin-3-yl)methyl]phenyl]-3-(4-methyl-1H-benzotriazol-5-yl)propanoate or chloro or bromoalkyl ethyl 3-[3-[(6-hydroxy-2,2-dioxo-1,4-dihydro-2,1,3-benzothiadiazin-3-yl)methyl]phenyl]-3-(4-methyl-1H-benzotriazol-5-yl)propanoate (1 eq., 0.055 mmol) in MeCN (16 mL), Cs<sub>2</sub>CO<sub>3</sub> (1-3 eq., 11 mg, 0.055 mmol) was added and the mixture was stirred at RT-80 °C for 4-36 h. After completion of the reaction, water (10 mL) was added to the mixture, and the MeCN was evaporated under reduced pressure. The residue was extracted with DCM (3x10 mL) and the combined organic layers were washed with water. The organic layer was dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, the filtrate was concentrated to dryness to give the title compound, which was purified by normal phase silica gel chromatography, or by reversed-phase chromatography using water-MeCN gradient elution (95:5 to 0:100) to give the title compound.

### **GENERAL PROCEDURE 12**

To the solution of the macrocyclic ester (1 eq., 0.067 mmol) in a mixture of THF (0.67 mL), MeOH or EtOH (0.17 mL) and water (0.34 mL), lithium hydroxyde (3 eq.-4 eq., 4.8 mg, 0.20 mmol) was added. The reaction mixture was stirred at RT-80 °C for 2-30 h. After completion of the reaction, citric acid solution (10%) or 1 M aq. HCl was added to the reaction mixture, and the neutralized mixture was extracted with DCM three times. The organic layer was dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, and the filtrate was concentrated. The residue was purified by preparative reversed-phase chromatography using water-MeCN gradient elution (95:5 to 0:100) to give the title compound.

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**EXAMPLE 1 :** [4,32-Dimethyl-28,28-dioxo-22,27-dioxa-28 $\lambda^6$ -thia-1,14,15,16-tetraazahexacyclo[21.5.3.1<sup>3,7</sup>.1<sup>9,13</sup>.0<sup>12,16</sup>.0<sup>26,30</sup>]tritiaconta-3(33),4,6,9(32),10,12,14,23,25,30-decaen-8-yl]acetic acid



5

#### STEP A1 : Preparation of 5-(3-methyl-2-nitroanilino)pentan-1-ol

Using General Procedure 1 STEP 1 starting from 1-fluoro-3-methyl-2-nitro-benzene (1 eq., 10.0 g, 7.85 mL, 64.5 mmol) and 5-aminopentan-1-ol (3 eq., 19.950 g, 21 mL, 193.5 mmol) as reactants, the title compound (12.6 g, 82% yield) was obtained.

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<sup>1</sup>H-NMR (400 MHz, DMSO-d<sub>6</sub>)  $\delta$  ppm: 7.26 (t, 1 H), 6.76 (d, 1 H), 6.54 (d, 1 H), 6.39 (t, 2 H), 4.34 (t, 1 H), 3.39 (q, 2 H), 3.16 (q, 2 H), 2.3 (s, 2 H), 1.55 (s, 2 H), 1.44 (m, 2 H), 1.34 (m, 2 H)

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#### STEP A2 : Preparation of 5-(4-bromo-3-methyl-2-nitroanilino)pentyl acetate

Using General Procedure 1 STEP 2 starting from 5-(3-methyl-2-nitroanilino)pentan-1-ol (8 g, 34 mmol) as a reactant, the title compound (12.6 g orange oil, quant.) was obtained.

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<sup>1</sup>H-NMR (400 MHz, DMSO-d<sub>6</sub>)  $\delta$  ppm: 7.5 (d, 1 H), 6.72 (d, 1 H), 6.12 (tl, 1 H), 4 (t, 2 H), 3.15 (q, 2 H), 2.25 (s, 3 H), 2 (s, 3 H), 1.6-1.3 (m, 6 H)

#### STEP A3 : Preparation of 5-(2-amino-4-bromo-3-methylanilino)pentyl acetate

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Using General Procedure 1 STEP 3 starting from 5-(4-bromo-3-methyl-2-nitroanilino)pentyl acetate (12.6 g, 35.1 mmol) as a reactant, the title compound (11.7 g orange solid, 91% yield) was obtained.

<sup>1</sup>H-NMR (400 MHz, DMSO-d<sub>6</sub>) δ ppm: 6.7 (d, 1 H), 6.25 (d, 1 H), 5.8 (m, 3 H), 4 (t, 2 H), 3 (t, 2 H), 2.2 (s, 3 H), 2.01 (s, 3 H), 1.65-1.4 (m, 6 H)

#### STEP A4 : Preparation of 5-(5-bromo-4-methyl-1*H*-benzotriazol-1-yl)pentyl acetate

Using General Procedure 1 STEP 4 starting from 5-(2-amino-4-bromo-3-methylanilino)pentyl acetate (12 g, 32 mmol) as a reactant, the title compound (7.5 g orange oil, 69% yield) was obtained.

<sup>1</sup>H-NMR (400 MHz, DMSO-d<sub>6</sub>) δ ppm: 7.7 (2d, 2 H), 4.7 (t, 2 H), 3.97 (t, 2 H), 2.71 (s, 3 H), 1.99 (s, 3 H), 1.95 (m, 2 H), 1.6 (m, 2 H), 1.29 (m, 2 H)

#### STEP A5 : Preparation of 5-(5-bromo-4-methyl-1*H*-benzotriazol-1-yl)pentan-1-ol

Using General Procedure 1 STEP 5 starting from 5-(5-bromo-4-methyl-1*H*-benzotriazol-1-yl)pentyl acetate (7.5 g, 22 mmol) as a reactant, the title compound (6.7 g orange oil, quant.) was obtained.

<sup>1</sup>H-NMR (400 MHz, DMSO-d<sub>6</sub>) δ ppm: 7.7 (2d, 2 H), 4.7 (t, 2 H), 4.35 (m, 1 H), 3.35 (t, 2 H), 2.71 (s, 3 H), 1.9 (m, 2 H), 1.45 (m, 2 H), 1.28 (m, 2 H)

#### STEP A6 : Preparation of 5-bromo-1-{5-[(4-methoxyphenyl)methoxy]pentyl}-4-methyl-1*H*-benzotriazole

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Using General Procedure 1 STEP 6 starting from 5-(5-bromo-4-methyl-1*H*-benzotriazol-1-yl)pentan-1-ol (3.0 g, 10 mmol) as a reactant, the title compound (3 g yellow oil, 72% yield) was obtained.

<sup>1</sup>H-NMR (400 MHz, DMSO-d<sub>6</sub>) δ ppm: 7.7 (2d, 2 H), 7.15 (d, 2 H), 6.85 (d, 2 H), 4.7 (t, 2 H), 4.3 (s, 2 H), 3.75 (s, 3 H), 3.32 (t, 2 H), 2.71 (s, 3 H), 1.9 (m, 2 H), 1.52 (m, 2 H), 1.28 (m, 2 H)

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**STEP A7 : Preparation of ethyl (2E)-3-(1-{5-[(4-methoxyphenyl)methoxy]pentyl}-4-methyl-1H-benzotriazol-5-yl)prop-2-enoate**

5 Using General Procedure 1 STEP 7 starting from 5-bromo-1-{5-[(4-methoxyphenyl)methoxy]pentyl}-4-methyl-1H-benzotriazole (3 g, 7.1 mmol) as a reactant, the title compound (3 g yellow solid, 91% yield) was obtained.

<sup>1</sup>H-NMR (500 MHz, DMSO-d<sub>6</sub>) δ ppm: 8.03 (d, 1 H), 7.96 (d, 1 H), 7.73 (d, 1 H), 7.16 (d, 2 H), 6.86 (d, 2 H), 6.64 (d, 1 H), 4.7 (t, 2 H), 4.3 (s, 2 H), 4.22 (q, 2 H), 3.73 (s, 3 H), 3.33 (t, 2 H), 2.81 (s, 3 H), 1.9 (m, 2 H), 1.53 (m, 2 H), 1.28 (t, 3 H), 1.26 (m, 2 H)

**STEP C1 : Preparation of 6-(benzyloxy)-2H-1,2λ<sup>6</sup>,3-benzoxathiazine-2,2-dione**

Using General Procedure 4 STEP 2 starting from 5-(benzyloxy)-2-hydroxybenzaldehyde (1 eq., 5.3 g, 23 mmol) as a reactant, the title compound (6.48 g yellow solid, 96% yield) was obtained.

<sup>1</sup>H-NMR (400 MHz, CDCl<sub>3</sub>) δ ppm: 8.6 (s, 1 H), 7.4 (m, 5 H), 7.35 (dd, 1 H), 7.3 (d, 1 H), 7.15 (d, 1 H), 5.1 (s, 2 H)

**STEP C2 : Preparation of 6-(benzyloxy)-3,4-dihydro-2H-1,2λ<sup>6</sup>,3-benzoxathiazine-2,2-dione**

Using General Procedure 4 STEP 3 starting from 6-(benzyloxy)-2H-1,2λ<sup>6</sup>,3-benzoxathiazine-2,2-dione (1 eq., 6.48 g, 22.4 mmol) as a reactant, the title compound (5.9 g, yellow solid, 90% yield) was obtained.

<sup>1</sup>H-NMR (400 MHz, DMSO-d<sub>6</sub>) δ ppm: 8.4 (sl, 1 H), 7.45 (d, 2 H), 7.4 (t, 2 H), 7.3 (t, 1 H), 7 (m, m H), 5.1 (s, 2 H), 4.5 (s, 2 H)

**STEP 1 : Preparation of ethyl 3-[3-(hydroxymethyl)-4-methylphenyl]-3-(1-{5-[(4-methoxyphenyl)methoxy]pentyl}-4-methyl-1H-benzotriazol-5-yl)propanoate**

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Using General Procedure 6 starting from (ethyl (2*E*)-3-(1-{5-[(4-methoxyphenyl)methoxy]pentyl}-4-methyl-1*H*-benzotriazol-5-yl)prop-2-enoate (1 eq., 4 g, 4.6 mmol), and [2-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]methanol (1.5 eq., 1.7 g, 6.9 mmol) as reactants, the title compound (0.96 g, 38% yield) was obtained.

<sup>1</sup>H-NMR (400 MHz, DMSO-d<sub>6</sub>) δ ppm: 7.6 (d, 1 H), 7.48 (d, 1 H), 7.25 (d, 1 H), 7.18 (d, 2 H), 7.08 (dd, 1 H), 7 (d, 1 H), 6.88 (d, 2 H), 4.98 (t, 1 H), 4.82 (t, 1 H), 4.61 (t, 2 H), 4.4 (d, 2 H), 4.3 (s, 2 H), 3.92 (q, 2 H), 3.71 (s, 3 H), 3.3 (t, 2 H), 3.11 (2dd, 2 H), 2.75 (s, 3 H), 2.15 (s, 3 H), 1.88 (m, 2 H), 1.52 (m, 2 H), 1.28 (m, 2 H), 1 (t, 3 H);

**STEP 2 : Preparation of ethyl 3-(3-{[6-(benzyloxy)-2,2-dioxo-2*H*-1,2λ<sup>6</sup>,3-benzoxathiazin-3(4*H*)-yl]methyl}-4-methylphenyl)-3-(1-{5-[(4-methoxyphenyl)methoxy]pentyl}-4-methyl-1*H*-benzotriazol-5-yl)propanoate**

Using General Procedure 7 starting from ethyl 3-[3-(hydroxymethyl)-4-methylphenyl]-3-(1-{5-[(4-methoxyphenyl)methoxy]pentyl}-4-methyl-1*H*-benzotriazol-5-yl)propanoate (1 eq., 0.96 g, 1.6 mmol), and 6-(benzyloxy)-3,4-dihydro-2*H*-1,2λ<sup>6</sup>,3-benzoxathiazine-2,2-dione (1.5 eq., 0.7 g, 2.4 mmol) as reactants, the title compound (90% yield) was obtained.

<sup>1</sup>H-NMR (400 MHz, DMSO-d<sub>6</sub>) δ ppm: 1.16 (m., 3 H) 1.21 - 1.29 (m, 1 H) 1.44 - 1.56 (m, 1 H) 1.78 - 1.89 (m, 1 H) 2.21 (s, 1 H) 2.76 (s, 1 H) 3.16 (dd, J=7.95, 4.77 Hz, 1 H) 3.26 - 3.29 (m, 1 H) 3.92 (q, J=7.09 Hz, 2 H) 4.21 (s, 2 H) 4.28 (s, 2 H) 4.42 (s, 2 H) 4.59 (t, J=6.91 Hz, 2 H) 4.85 (t, J=7.95 Hz, 1 H) 5.10 (s, 2 H) 6.82 - 6.88 (m, 2 H) 6.94 (d, J=2.81 Hz, 1 H) 7.03 - 7.10 (m, 1 H) 7.10 - 7.17 (m, 4 H) 7.17 - 7.21 (m, 1 H) 7.22 (s, 1 H) 7.31 - 7.37 (m, 1 H) 7.37 - 7.43 (m, 2 H) 7.45 (s, 2 H) 7.48 (d, J=8.44 Hz, 2 H) 7.56 - 7.61 (m, 1 H)

**STEP 3 : Preparation of ethyl 3-{3-[(6-hydroxy-2,2-dioxo-2*H*-1,2λ<sup>6</sup>,3-benzoxathiazin-3(4*H*)-yl)methyl]-4-methylphenyl}-3-[1-(5-hydroxypentyl)-4-methyl-1*H*-benzotriazol-5-yl]propanoate**



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Using General Procedure 8 starting from ethyl 3-(3-{{[6-(benzyloxy)-2,2-dioxo-2*H*-1,2λ<sup>6</sup>,3-benzoxathiazin-3(4*H*)-yl]methyl}-4-methylphenyl}-3-(1-{5-[(4-methoxyphenyl)methoxy]pentyl}-4-methyl-1*H*-benzotriazol-5-yl)propanoate (1 eq., 2 g, 1.4 mmol) as a reactant, the title compound (830 mg yellow oil, 90% yield) was obtained.

5 <sup>1</sup>H-NMR (400 MHz, DMSO-d<sub>6</sub>) δ ppm: 9.7/4.38 (2m, 2 H), 7.61 (d, 1 H), 7.5 (d, 1 H), 7.21 (d, 1 H), 7.2 (dd, 1 H), 7.12 (d, 1 H), 6.99 (d, 1 H), 6.8 (dd, 1 H), 6.6 (d, 1 H), 4.82 (t, 1 H), 4.61 (t, 2 H), 4.39 (s, 2 H), 4.29 (m, 2 H), 3.95 (q, 2 H), 3.31 (t, 2 H), 3.18 (m, 2 H), 2.75 (s, 3 H), 2.2 (s, 3 H), 1.88 (m, 2 H), 1.4 (m, 2 H), 1.25 (m, 2 H), 1 (t, 3 H)

10 **STEP 4 : Preparation of ethyl 3-[1-(5-bromopentyl)-4-methyl-1*H*-benzotriazol-5-yl]-3-{{[6-hydroxy-2,2-dioxo-2*H*-1,2λ<sup>6</sup>,3-benzoxathiazin-3(4*H*)-yl]methyl}-4-methylphenyl}propanoate**

Using General Procedure 9 starting from ethyl 3-{3-[(6-hydroxy-2,2-dioxo-2*H*-1,2λ<sup>6</sup>,3-benzoxathiazin-3(4*H*)-yl)methyl]-4-methylphenyl}-3-[1-(5-hydroxypentyl)-4-methyl-1*H*-benzotriazol-5-yl]propanoate (1 eq., 0.8 g, 1.3 mmol) as a reactant, the title compound (710 mg white solid, 80% yield) was obtained.

15 <sup>1</sup>H-NMR (400 MHz, DMSO-d<sub>6</sub>) δ ppm: 9.7 (m, 1 H), 7.61 (d, 1 H), 7.5 (d, 1 H), 7.21 (d, 1 H), 7.2 (dd, 1 H), 7.12 (d, 1 H), 6.99 (d, 1 H), 6.8 (dd, 1 H), 6.6 (d, 1 H), 4.82 (t, 1 H), 4.65 (t, 2 H), 4.39 (s, 2 H), 4.29 (m, 2 H), 3.92 (q, 2 H), 3.45 (t, 2 H), 3.18 (m, 2 H), 2.75 (s, 3 H), 2.21 (s, 3 H), 1.9 (m, 2 H), 1.8 (m, 2 H), 1.35 (m, 2 H), 1 (t, 3 H)

25 **STEP 5 : Preparation of ethyl [4,32-dimethyl-28,28-dioxo-22,27-dioxa-28λ<sup>6</sup>-thia-1,14,15,16-tetraazahexacyclo[21.5.3.1<sup>3,7</sup>.1<sup>9,13</sup>.0<sup>12,16</sup>.0<sup>26,30</sup>]tritiaconta-3(33),4,6,9(32),10,12,14,23,25,30-decaen-8-yl]acetate**

Using General Procedure 11 starting from ethyl 3-[1-(5-bromopentyl)-4-methyl-1*H*-benzotriazol-5-yl]-3-{{[6-hydroxy-2,2-dioxo-2*H*-1,2λ<sup>6</sup>,3-benzoxathiazin-3(4*H*)-yl]methyl}-4-methylphenyl} propanoate (1 eq., 0.7 g, 0.99 mmol) as a reactant, the title compound (620 mg yellow oil, 93% yield) was obtained.

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<sup>1</sup>H-NMR (400 MHz, DMSO-d<sub>6</sub>) δ ppm: 7.65 (d, 1 H), 7.52 (d, 1 H), 7.5 (dd, 1 H), 7.3 (d, 1 H), 7.05 (d, 1 H), 6.9 (dd, 1 H), 6.78 (d, 1 H), 6.12 (d, 1 H), 4.8 (t, 1 H), 4.7 (t, 2 H), 4.2/3.9 (m, 2 H), 4.15/4 (m, 2 H), 3.9 (m, 2 H), 3.85 (m, 2 H), 3.07 (m, 2 H), 2.68 (s, 3 H), 2.35 (s, 3 H), 2 (m, 2 H), 1.75 (m, 2 H), 1.5/1.4 (m, 2 H), 1 (t, 3 H)

5

#### STEP 6 : Preparation of EXAMPLE 1

Using General Procedure 12 starting from ethyl [4,32-dimethyl-28,28-dioxo-22,27-dioxa-28λ<sup>6</sup>-thia-1,14,15,16-tetraazahexacyclo[21.5.3.1<sup>3,7</sup>.1<sup>9,13</sup>.0<sup>12,16</sup>.0<sup>26,30</sup>]tritiaconta-

10 3(33),4,6,9(32),10,12,14,23,25,30-decaen-8-yl]acetate (1 eq., 0.62 g, 0.92 mmol) as a reactant, the title compound (291 mg white solid, 55% yield) was obtained.

The enantiopure products were obtained by chromatographic separation on chiral column.

#### Example 1a (E1)

15 HRMS calculated for C<sub>30</sub>H<sub>32</sub>N<sub>4</sub>O<sub>6</sub>S: 576.2042; [M+H]<sup>+</sup> found: 577.2115 (δ=-0.1 ppm)

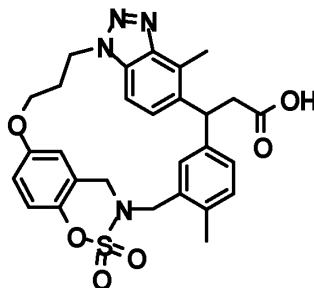
#### Example 1b (E2)

HRMS calculated for C<sub>30</sub>H<sub>32</sub>N<sub>4</sub>O<sub>6</sub>S: 576.2042; [M+H]<sup>+</sup> found: 577.2113 (δ=-0.4 ppm)

20 <sup>1</sup>H-NMR (400 MHz, DMSO-d<sub>6</sub>) δ ppm: 11.55 (m, 1 H), 7.62 (d, 1 H), 7.5 (d, 2 H), 7.29 (d, 1 H), 7.02 (d, 1 H), 6.9 (dd, 1 H), 6.72 (d, 1 H), 6.11 (d, 1 H), 4.8 (t, 1 H), 4.7 (t, 2 H), 4.2/3.9 (2d, 2 H), 4.11/4 (2d, 2 H), 3.9/3.8 (2m, 2 H), 2.92 (2dd, 2 H), 2.65 (s, 3 H), 2.31 (s, 3 H), 1.99 (m, 2 H), 1.72 (m, 2 H), 1.48/1.38 (2m, 2 H)

25 **EXAMPLE 2 : [4,30-Dimethyl-26,26-dioxo-20,25-dioxa-26λ<sup>6</sup>-thia-1,14,15,16-tetraazahexacyclo[19.5.3.1<sup>3,7</sup>.1<sup>9,13</sup>.0<sup>12,16</sup>.0<sup>24,28</sup>]hentriaconta-3(31),4,6,9(30),10,12,14,21,23,28-decaen-8-yl]acetic acid**

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#### STEP A1 : Preparation of *N*-[3-(benzyloxy)propyl]-3-methyl-2-nitroaniline

Using General Procedure 2 STEP 1 starting from 1-fluoro-3-methyl-2-nitro-benzene (1 eq., 1.93 mmol) and 3-benzyloxypropan-1-amine (1.2 eq., 383 mg, 2.32 mmol) as reactants, the title compound (375 mg, 64% yield) was obtained.

<sup>1</sup>H-NMR (400 MHz, DMSO-d<sub>6</sub>) δ ppm: 7.37-7.26 (m, 5 H), 7.26 (t, 1 H), 6.77 (d, 1 H), 6.55 (d, 1 H), 6.47 (t, 1 H), 4.47 (s, 2 H), 3.51 (t, 2 H), 2.29 (s, 2 H), 2.26 (q, 2 H), 1.83 (m, 2 H)

#### 10 STEP A2 : Preparation of *N*-[3-(benzyloxy)propyl]-4-bromo-3-methyl-2-nitroaniline

Using General Procedure 2 STEP 2 starting from *N*-[3-(benzyloxy)propyl]-3-methyl-2-nitroaniline (6.5 g, 22 mmol) as a reactant, the title compound (6.54 g, 80% yield) was obtained.

<sup>1</sup>H-NMR (400 MHz, DMSO-d<sub>6</sub>) δ ppm: 7.5 (d, 1 H), 7.3 (m, 5 H), 6.72 (d, 1 H), 6.18 (t), 4.45 (s, 2 H), 3.48 (t, 2 H), 3.22 (q, 2 H), 2.25 (s, 3 H), 1.8 (m, 2 H)

#### STEP A3 : Preparation of *N*<sup>1</sup>-[3-(benzyloxy)propyl]-4-bromo-3-methylbenzene-1,2-diamine

20 Using General Procedure 2 STEP 3 starting from *N*-[3-(benzyloxy)propyl]-4-bromo-3-methyl-2-nitroaniline (6.5 g, 17 mmol) as a reactant, the title compound (5.4 g, 75% yield) was obtained.

<sup>1</sup>H-NMR (400 MHz, DMSO-d<sub>6</sub>) δ ppm: 7.39-7.24 (s, 5 H), 6.71 (d, 1 H), 6.26 (d, 1 H), 4.62-4.54 (m, 3 H), 4.48 (s, 2 H), 3.55 (t, 2 H), 3.08 (q, 2 H), 2.16 (s, 3 H), 1.86 (m, 2 H)

**STEP A4 : Preparation of 1-[3-(benzyloxy)propyl]-5-bromo-4-methyl-1H-benzotriazole**

Using General Procedure 2 STEP 4 starting from *N*<sup>1</sup>-[3-(benzyloxy)propyl]-4-bromo-3-methylbenzene-1,2-diamine (5.4 g, 13 mmol) as a reactant, the title compound (1.09 g, 23% yield) was obtained.

<sup>1</sup>H-NMR (400 MHz, DMSO-d<sub>6</sub>) δ ppm: 7.68/7.65 (d, 2 H), 7.34-7.2 (m, 5 H), 4.78 (t, 2 H), 4.38 (s, 2 H), 3.41 (t, 2 H), 2.71 (s, 3 H), 2.18 (m, 2 H)

10 **STEP A5 : Preparation of ethyl (2E)-3-{1-[3-(benzyloxy)propyl]-4-methyl-1H-benzotriazol-5-yl}prop-2-enoate**

Using General Procedure 2 STEP 5 starting from 1-[3-(benzyloxy)propyl]-5-bromo-4-methyl-1H-benzotriazole (1.05 g, 2.91 mmol) as a reactant, the title compound (1.18 g, 70% yield) was obtained.

<sup>1</sup>H-NMR (400 MHz, DMSO-d<sub>6</sub>) δ ppm: 1.28 (t, J=7.09 Hz, 2 H) 2.14 - 2.23 (m, 3 H) 3.41 (td, J=5.96, 3.00 Hz, 3 H) 4.22 (q, J=7.17 Hz, 2 H) 4.36 - 4.41 (m, 3 H) 4.78 (t, J=6.79 Hz, 3 H) 6.65 (d, J=15.77 Hz, 1 H) 7.28 (s, 7 H) 7.69 (d, J=8.80 Hz, 1 H) 7.95 - 7.97 (m, 1 H) 8.03 (d, J=15.89 Hz, 1 H)

20

**STEP 1 : Preparation of ethyl 3-{1-[3-(benzyloxy)propyl]-4-methyl-1H-benzotriazol-5-yl}-3-[3-(hydroxymethyl)-4-methylphenyl]propanoate**

Using General Procedure 6 starting from ethyl (2E)-3-{1-[3-(benzyloxy)propyl]-4-methyl-1H-benzotriazol-5-yl}prop-2-enoate (1 eq.), and [2-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]methanol (1.5 eq.) as reactants, the title compound (yellow oil, 44% yield) was obtained.

<sup>1</sup>H-NMR (400 MHz, DMSO-d<sub>6</sub>) δ ppm: 7.55 (d, 1 H), 7.45 (d, 1 H), 7.25 (m, 6 H), 7.1 (dd, 1 H), 7.01 (d, 1 H), 4.81 (t, 1 H), 4.81 (t, 1 H), 4.7 (t, 2 H), 4.4 (d+s, 4 H), 3.92 (q, 2 H), 3.4 (t, 2 H), 3.12 (2dd, 2 H), 2.75 (s, 3 H), 2.15 (m+s, 5 H), 1 (t, 3 H)

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**STEP 2 : Preparation of ethyl 3-(3-{[6-(benzyloxy)-2,2-dioxo-2*H*-1,2λ<sup>6</sup>,3-benzoxathiazin-3(4*H*)-yl]methyl}-4-methylphenyl)-3-{1-[3-(benzyloxy)propyl]-4-methyl-1*H*-benzotriazol-5-yl}propanoate**

5

Using General Procedure 7 starting from ethyl 3-{1-[3-(benzyloxy)propyl]-4-methyl-1*H*-benzotriazol-5-yl}-3-[3-(hydroxymethyl)-4-methylphenyl]propanoate (1 eq.), and 6-(benzyloxy)-3,4-dihydro-2*H*-1,2λ<sup>6</sup>,3-benzoxathiazine-2,2-dione (1.5 eq.) as reactants, the title compound (94% yield) was obtained.

10 **<sup>1</sup>H-NMR** (400 MHz, DMSO-d<sub>6</sub>) δ ppm: 0.98 (t, J=7.09 Hz, 3 H) 2.13 (quint, J=6.36 Hz, 2 H) 2.22 (s, 3 H) 2.76 (s, 3 H) 3.17 (dd, J=8.01, 3.36 Hz, 2 H) 3.36 (t, J=6.05 Hz, 2 H) 3.92 (q, J=7.13 Hz, 2 H) 4.21 (s, 2 H) 4.37 (s, 2 H) 4.41 (s, 2 H) 4.68 (t, J=6.79 Hz, 2 H) 4.85 (t, J=8.01 Hz, 1 H) 5.10 (s, 2 H) 6.94 (d, J=2.81 Hz, 1 H) 7.03 - 7.09 (m, 1 H) 7.10 - 7.16 (m, 2 H) 7.16 - 7.31 (m, 7 H) 7.32 - 7.37 (m, 1 H) 7.37 - 7.43 (m, 1 H) 7.44 - 7.47 (m, 1 H) 7.48 (d, J=8.80 Hz, 1 H) 7.53 - 7.59 (m, 1 H)

15

**STEP 3 : Preparation of ethyl 3-[1-(3-bromopropyl)-4-methyl-1*H*-benzotriazol-5-yl]-3-{3-[(6-hydroxy-2,2-dioxo-2*H*-1,2λ<sup>6</sup>,3-benzoxathiazin-3(4*H*)-yl)methyl]-4-methylphenyl}propanoate**

20

Using General Procedure 8 starting from ethyl 3-(3-{[6-(benzyloxy)-2,2-dioxo-2*H*-1,2λ<sup>6</sup>,3-benzoxathiazin-3(4*H*)-yl]methyl}-4-methylphenyl)-3-{1-[3-(benzyloxy)propyl]-4-methyl-1*H*-benzotriazol-5-yl}propanoate (1 eq.) as reactant ethyl 3-{3-[(6-hydroxy-2,2-dioxo-2*H*-1,2λ<sup>6</sup>,3-benzoxathiazin-3(4*H*)-yl)methyl]-4-methylphenyl}-3-[1-(3-hydroxypropyl)-4-methyl-1*H*-benzotriazol-5-yl]propanoate (65% yield) was obtained. The crude product was reacted using General Procedure 9, resulting in the title compound (69% yield).

25

**<sup>1</sup>H-NMR** (400 MHz, DMSO-d<sub>6</sub>) δ ppm: 9.65 (s, 1 H), 7.62 (d, 1 H), 7.51 (d, 1 H), 7.2 (d, 1 H), 7.18 (dd, 1 H), 7.1 (d, 1 H), 7 (d, 1 H), 6.8 (dd, 1 H), 6.6 (d, 1 H), 4.85 (t, 1 H), 4.75 (t, 2 H), 4.38 (s, 2 H), 4.2 (m, 2 H), 3.92 (q, 2 H), 3.48 (t, 2 H), 3.18 (d, 2 H), 2.75 (s, 3 H), 2.42 (m, 2 H), 2.21 (s, 3 H), 1 (t, 3 H)

30

**STEP 4 : Preparation of ethyl [4,30-dimethyl-26,26-dioxo-20,25-dioxa-26 $\lambda^6$ -thia-1,14,15,16-tetraazahexacyclo[19.5.3.1<sup>3,7</sup>.1<sup>9,13</sup>.0<sup>12,16</sup>.0<sup>24,28</sup>]hentriaconta-3(31),4,6,9(30),10,12,14,21,23,28-decaen-8-yl]acetate**

5

Using General Procedure 11 starting from ethyl 3-[1-(3-bromopropyl)-4-methyl-1*H*-benzotriazol-5-yl]-3-{3-[(6-hydroxy-2,2-dioxo-2*H*-1,2 $\lambda^6$ ,3-benzoxathiazin-3(4*H*)-yl)methyl]-4-methylphenyl}propanoate (1 eq.) as a reactant, the title compound (96% yield) was obtained. <sup>1</sup>H-NMR (400 MHz, DMSO-d<sub>6</sub>)  $\delta$  ppm: 7.54 (d, 1 H), 7.48 (dd, 1 H), 7.44 (d, 1 H), 7.28 (d, 1 H), 7.01 (d, 1 H), 6.85 (dd, 1 H), 6.47 (d, 1 H), 5.2 (d, 1 H), 4.87 (m, 2 H), 4.76 (t, 1 H), 4.36/3.64 (d, 2 H), 4.13/3.44 (d, 2 H), 4.01/3.7 (tt, 2 H), 3.91 (q, 2 H), 3.03 (d, 2 H), 2.63 (s, 3 H), 2.47/2.38 (m, 2 H), 2.32 (s, 3 H), 1 (t, 3 H)

10

**STEP 5 : Preparation of EXAMPLE 2**

15

Using General Procedure 12 starting from ethyl [4,30-dimethyl-26,26-dioxo-20,25-dioxa-26 $\lambda^6$ -thia-1,14,15,16-tetraazahexacyclo[19.5.3.1<sup>3,7</sup>.1<sup>9,13</sup>.0<sup>12,16</sup>.0<sup>24,28</sup>]hentriaconta-3(31),4,6,9(30),10,12,14,21,23,28-decaen-8-yl]acetate (1 eq.) as a reactant, the title compound (white solid, 70% yield) was obtained as a racemic compound.

20

**HRMS** calculated for C<sub>28</sub>H<sub>28</sub>N<sub>4</sub>O<sub>6</sub>S: 548.1730; [M+H]<sup>+</sup> found: 549.1805 ( $\delta$ =0.5 ppm)

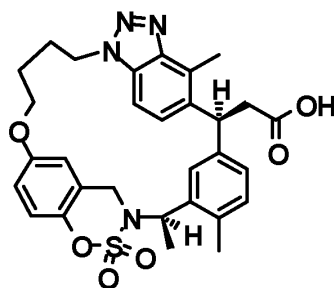
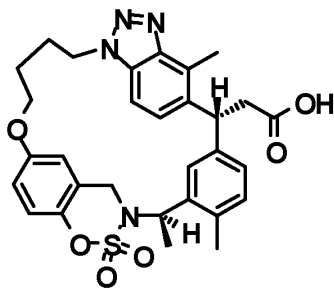
<sup>1</sup>H-NMR (400 MHz, DMSO-d<sub>6</sub>)  $\delta$  ppm: 12.2 (m, 1 H), 7.55 (d, 1 H), 7.45 (dd, 1 H), 7.4 (d, 1 H), 7.25 (d, 1 H), 7 (d, 1 H), 6.85 (dd, 1 H), 6.43 (d, 1 H), 5.22 (d, 1 H), 4.85 (m, 2 H), 4.75 (t, 1 H), 4.35/3.65 (m, 2 H), 4.15/3.45 (m, 2 H), 4/3.7 (m, 2 H), 2.95 (d, 2 H), 2.65 (s, 3 H), 2.4 (m, 2 H), 2.3 (s, 3 H)

25

**EXAMPLE 3 : [(2*R*,8*R*)-2,4,31-Trimethyl-27,27-dioxo-21,26-dioxa-27 $\lambda^6$ -thia-1,14,15,16-tetraazahexacyclo[20.5.3.1<sup>3,7</sup>.1<sup>9,13</sup>.0<sup>12,16</sup>.0<sup>25,29</sup>]dotriaconta-3(32),4,6,9(31),10,12,14,22,24,29-decaen-8-yl]acetic acid and**

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[(2*R*,8*S*)-2,4,31-trimethyl-27,27-dioxo-21,26-dioxa-27 $\lambda^6$ -thia-1,14,15,16-tetraazahexacyclo[20.5.3.1<sup>3,7</sup>.1<sup>9,13</sup>.0<sup>12,16</sup>.0<sup>25,29</sup>]dotriaconta-3(32),4,6,9(31),10,12,14,22,24,29-decaen-8-yl]acetic acid



5

#### STEP A1 : Preparation of 4-(3-methyl-2-nitroanilino)butan-1-ol

Using General Procedure 1 STEP 1 starting from 1-fluoro-3-methyl-2-nitro-benzene (1 eq.) and 4-aminobutan-1-ol (3 eq.) as reactants, the title compound (44% yield) was obtained.

<sup>1</sup>H-NMR (400 MHz, DMSO-d<sub>6</sub>) δ ppm: 7.28 (t, 1 H), 6.78 (d, 1 H), 6.52 (d, 1 H), 6.4 (t, 1 H), 4.4 (t, 1 H), 3.41 (q, 2 H), 3.2 (q, 2 H), 2.3 (s, 3 H), 1.58 (m, 2 H), 1.48 (m, 2 H)

#### STEP A2 : Preparation of 4-(4-bromo-3-methyl-2-nitroanilino)butyl acetate

15

Using General Procedure 1 STEP 2 starting from 4-(3-methyl-2-nitroanilino)butan-1-ol (1 eq.) as a reactant, the title compound (orange oil, 93% yield) was obtained.

<sup>1</sup>H-NMR (400 MHz, DMSO-d<sub>6</sub>) δ ppm: 7.52 (d, 1 H), 6.72 (d, 1 H), 6.15 (t, 1 H), 4 (t, 2 H), 3.15 (q, 2 H), 2.25 (s, 3 H), 2 (s, 3 H), 1.55 (m, 4 H)

20

#### STEP A3 : Preparation of 4-(2-amino-4-bromo-3-methylanilino)butyl acetate

Using General Procedure 1 STEP 3 starting from 4-(4-bromo-3-methyl-2-nitroanilino)butyl acetate (1 eq.) as a reactant, the title compound (72% yield) was obtained.

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**<sup>1</sup>H-NMR** (400 MHz, DMSO-d<sub>6</sub>) δ ppm: 6.7 (d, 1 H), 6.25 (d, 1 H), 5.2-4.5 (ml, 3 H), 4.01 (t, 2 H), 3 (t, 2 H), 2.19 (s, 3 H), 2 (s, 3 H), 1.7-1.5 (m, 4 H)

**STEP A4 : Preparation of 4-(5-bromo-4-methyl-1*H*-benzotriazol-1-yl)butyl acetate**

5

Using General Procedure 1 STEP 4 starting from 4-(2-amino-4-bromo-3-methylanilino)butyl acetate (1 eq.) as a reactant, the title compound (orange oil, 49% yield) was obtained.

**HRMS** calculated for C<sub>13</sub>H<sub>16</sub>BrN<sub>3</sub>O<sub>2</sub>: 325.0426; [M+H]<sup>+</sup> found: 326.0502 (δ=1.0 ppm)

10 **STEP A5 : Preparation of 4-(5-bromo-4-methyl-1*H*-benzotriazol-1-yl)butan-1-ol**

Using General Procedure 1 STEP 5 starting from 4-(5-bromo-4-methyl-1*H*-benzotriazol-1-yl)butyl acetate (1 eq.) as a reactant, the title compound (orange oil, 85% yield) was obtained.

15 **<sup>1</sup>H-NMR** (400 MHz, DMSO-d<sub>6</sub>) δ ppm: 7.7 (m, 2 H), 4.75 (t, 2 H), 4.45 (t, 1 H), 3.45 (q, 2 H), 2.75 (s, 3 H), 1.95 (m, 2 H), 1.4 (m, 2 H)

**STEP A6 : Preparation of 5-bromo-1-{4-[(4-methoxyphenyl)methoxy]butyl}-4-methyl-1*H*-benzotriazole**

20 Using General Procedure 1 STEP 6 starting from 4-(5-bromo-4-methyl-1*H*-benzotriazol-1-yl)butan-1-ol (1 eq.) as a reactant, the title compound (yellow oil, 74% yield) was obtained.

**<sup>1</sup>H-NMR** (400 MHz, DMSO-d<sub>6</sub>) δ ppm: 7.68 (s, 2 H), 7.19 (d, 2 H), 6.88 (d, 2 H), 4.71 (t, 2 H), 4.32 (s, 2 H), 3.73 (s, 3 H), 3.39 (t, 2 H), 2.72 (s, 3 H), 1.95 (quint, 2 H), 1.48 (quint, 2 H)

25 **STEP A7 : Preparation of ethyl (2*E*)-3-(1-{4-[(4-methoxyphenyl)methoxy]butyl}-4-methyl-1*H*-benzotriazol-5-yl)prop-2-enoate**

Using General Procedure 1 STEP 7 starting from 5-bromo-1-{4-[(4-methoxyphenyl)methoxy]butyl}-4-methyl-1*H*-benzotriazole (1 eq.) as a reactant, the title  
30 compound (yellow solid, 74% yield) was obtained.



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**<sup>1</sup>H-NMR** (400 MHz, DMSO-d<sub>6</sub>) δ ppm: 8.02 (d, 1 H), 7.95 (d, 1 H), 7.7 (d, 1 H), 7.19 (d, 2 H), 6.88 (d, 2 H), 6.65 (d, 1 H), 4.71 (t, 2 H), 4.32 (s, 2 H), 4.22 (q, 2 H), 3.73 (s, 3 H), 3.39 (t, 2 H), 2.81 (s, 3 H), 1.95 (m, 2 H), 1.49 (m, 2 H), 1.28 (t, 3 H)

5     **STEP 1 : Preparation of ethyl 3-{3-[(1*S*)-1-hydroxyethyl]-4-methylphenyl}-3-(1-{4-[(4-methoxyphenyl)methoxy]butyl}-4-methyl-1*H*-benzotriazol-5-yl)propanoate**

Using General Procedure 6 starting from ethyl (2*E*)-3-(1-{4-[(4-methoxyphenyl)methoxy]butyl}-4-methyl-1*H*-benzotriazol-5-yl)prop-2-enoate (1 eq.), and  
10     (1*S*)-1-[2-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]ethan-1-ol (2 eq.) as reactants, the title compound (yellow oil, 82% yield) was obtained.

**<sup>1</sup>H-NMR** (400 MHz, DMSO-d<sub>6</sub>) δ ppm: 0.99 (t, J=7.09 Hz, 3 H) 1.22 (dd, J=8.74, 6.42 Hz, 3 H) 1.42 - 1.53 (m, 2 H) 1.92 (quin, J=7.21 Hz, 2 H) 1.99 (s, 2 H) 2.19 (s, 3 H) 2.76 (d, J=3.79 Hz, 3 H) 3.09 - 3.16 (m, 2 H) 3.38 (t, J=6.30 Hz, 2 H) 3.73 (s, 3 H) 3.92 (q, J=7.09 Hz, 2 H)  
15     4.32 (s, 2 H) 4.64 (t, J=6.91 Hz, 2 H) 4.83 (dt, J=7.64, 3.88 Hz, 2 H) 4.92 - 5.01 (m, 1 H) 6.83 - 6.90 (m, 2 H) 6.95 - 7.01 (m, 1 H) 7.02 - 7.08 (m, 1 H) 7.19 (d, J=8.56 Hz, 2 H) 7.40 (d, J=1.71 Hz, 1 H) 7.43 - 7.49 (m, 1 H) 7.55 - 7.60 (m, 1 H)

20     **STEP 2 : Preparation of ethyl 3-(3-{(1*R*)-1-[6-(benzyloxy)-2,2-dioxo-2*H*-1,2λ<sup>6</sup>,3-benzoxathiazin-3(4*H*)-yl]ethyl}-4-methylphenyl)-3-(1-{4-[(4-methoxyphenyl)methoxy]butyl}-4-methyl-1*H*-benzotriazol-5-yl)propanoate**

Using General Procedure 7 starting from ethyl 3-{3-[(1*S*)-1-hydroxyethyl]-4-methylphenyl}-3-(1-{4-[(4-methoxyphenyl)methoxy]butyl}-4-methyl-1*H*-benzotriazol-5-yl)propanoate (1 eq.),  
25     and 6-(benzyloxy)-3,4-dihydro-2*H*-1,2λ<sup>6</sup>,3-benzoxathiazine-2,2-dione (1.5 eq.) as reactants, the title compound (69% yield) was obtained.

**<sup>1</sup>H-NMR** (400 MHz, DMSO-d<sub>6</sub>) δ ppm: 0.93 - 1.01 (m, 3 H) 1.36 - 1.49 (m, 5 H) 1.83 - 1.94 (m, 2 H) 2.28 (s, 3 H) 2.77 (d, J=4.65 Hz, 3 H) 3.17 - 3.24 (m, 2 H) 3.32 - 3.38 (m, 2 H) 3.72 (s, 3 H) 3.88 - 3.95 (m, 2 H) 4.29 (d, J=2.69 Hz, 2 H) 4.37 - 4.46 (m, 1 H) 4.56 - 4.65 (m, 2 H) 4.82  
30     - 4.91 (m, 1 H) 5.03 - 5.13 (m, 2 H) 5.27 (q, J=6.77 Hz, 1 H) 6.80 - 6.91 (m, 3 H) 6.95 - 7.07

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(m, 2 H) 7.07 - 7.15 (m, 2 H) 7.18 (d, J=8.44 Hz, 2 H) 7.30 - 7.48 (m, 6 H)

**STEP 3 : Preparation of ethyl 3-[1-(4-hydroxybutyl)-4-methyl-1*H*-benzotriazol-5-yl]-3-{3-[(1*R*)-1-(6-hydroxy-2,2-dioxo-2*H*-1,2λ<sup>6</sup>,3-benzoxathiazin-3(4*H*)-yl)ethyl]-4-methylphenyl}propanoate**

Using General Procedure 8 starting from ethyl 3-(3-{(1*R*)-1-[6-(benzyloxy)-2,2-dioxo-2*H*-1,2λ<sup>6</sup>,3-benzoxathiazin-3(4*H*)-yl]ethyl}-4-methylphenyl)-3-(1-{4-[(4-methoxyphenyl)methoxy] butyl}-4-methyl-1*H*-benzotriazol-5-yl)propanoate (1 eq.) as a reactant, the title compound (79% yield) was obtained.

<sup>1</sup>H-NMR (400 MHz, DMSO-d<sub>6</sub>) δ ppm: 1.00 (q, J=7.01 Hz, 3 H) 1.29 - 1.39 (m, 2 H) 1.39 - 1.46 (m, 3 H) 1.85 - 1.96 (m, 2 H) 2.28 (s, 3 H) 2.77 (s, 3 H) 3.22 (d, J=7.83 Hz, 2 H) 3.35 - 3.41 (m, 3 H) 3.94 (qd, J=7.11, 2.02 Hz, 2 H) 4.23 - 4.36 (m, 1 H) 4.37 (s, 1 H) 4.41 (t, J=5.14 Hz, 1 H) 4.65 (t, J=7.03 Hz, 2 H) 4.78 - 4.95 (m, 1 H) 5.26 (q, J=6.64 Hz, 1 H) 6.53 - 6.62 (m, 1 H) 6.69 - 6.76 (m, 1 H) 6.79 - 6.84 (m, 1 H) 6.88 - 6.94 (m, 1 H) 7.05 - 7.15 (m, 3 H) 7.47 (d, J=10.64 Hz, 1 H) 9.57 - 9.72 (m, 1 H)

**STEP 4 : Preparation of ethyl 3-[1-(4-bromobutyl)-4-methyl-1*H*-benzotriazol-5-yl]-3-{3-[(1*R*)-1-(6-hydroxy-2,2-dioxo-2*H*-1,2λ<sup>6</sup>,3-benzoxathiazin-3(4*H*)-yl)ethyl]-4-methylphenyl}propanoate**

Using General Procedure 9 starting from ethyl 3-[1-(4-hydroxybutyl)-4-methyl-1*H*-benzotriazol-5-yl]-3-{3-[(1*R*)-1-(6-hydroxy-2,2-dioxo-2*H*-1,2λ<sup>6</sup>,3-benzoxathiazin-3(4*H*)-yl)ethyl]-4-methylphenyl}propanoate (1 eq.) as a reactant, the title compound (colorless solid, 91% yield) was obtained.

<sup>1</sup>H-NMR (400 MHz, DMSO-d<sub>6</sub>) δ ppm: 9.63/9.62 (2s, 1 H), 7.64/7.59 (4d, 2 H), 7.48/7.45 (2s, 1 H), 7.11 (m, 2 H), 6.91 (d, 1 H), 6.73 (m, 1 H), 6.6/6.56 (2d, 1 H), 5.26 (m, 1 H), 4.88 (m, 1 H), 4.69 (t, 2 H), 4.37/4.31 (s+m, 2 H), 3.94 (2q, 2 H), 3.54 (t, 2 H), 3.23 (dl, 2 H), 2.77 (s, 3 H), 2.28 (s, 3 H), 1.99 (quint, 2 H), 1.77 (quint, 2 H), 1.43/1.41 (2d, 3 H)

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**STEP 5 : Preparation of ethyl [(2*R*)-2,4,31-trimethyl-27,27-dioxo-21,26-dioxa-27 $\lambda^6$ -thia-1,14,15,16-tetraazahexacyclo[20.5.3.1<sup>3,7</sup>.1<sup>9,13</sup>.0<sup>12,16</sup>.0<sup>25,29</sup>]dotriaconta-3(32),4,6,9(31),10,12,14,22,24,29-decaen-8-yl]acetate**

- 5 Using General Procedure 11 starting from ethyl 3-[1-(4-bromobutyl)-4-methyl-1*H*-benzotriazol-5-yl]-3-{3-[(1*R*)-1-(6-hydroxy-2,2-dioxo-2*H*-1,2 $\lambda^6$ ,3-benzoxathiazin-3(4*H*)-yl)ethyl]-4-methylphenyl} propanoate (1 eq.) as a reactant, the title compound (white solid, 91% yield) was obtained.

<sup>1</sup>**H-NMR** (400 MHz, DMSO-d<sub>6</sub>)  $\delta$  ppm: 1.03 (td, J=7.09, 3.30 Hz, 9 H) 1.23 - 1.30 (m, 7 H)  
 10 1.33 - 1.94 (m, 12 H) 2.25 - 2.35 (m, 11 H) 2.67 (s, 6 H) 2.96 - 3.15 (m, 5 H) 3.34 - 3.53 (m, 9 H) 3.62 - 3.75 (m, 4 H) 3.88 - 3.98 (m, 5 H) 3.99 - 4.11 (m, 4 H) 4.70 - 4.85 (m, 10 H) 4.92 (t, J=7.95 Hz, 2 H) 5.18 - 5.31 (m, 2 H) 5.72 (d, J=2.81 Hz, 1 H) 5.89 (br. s., 1 H) 6.74 - 6.78 (m, 1 H) 6.88 - 6.98 (m, 2 H) 7.17 (s, 1 H) 7.31 (d, J=8.07 Hz, 1 H) 7.44 (d, J=7.58 Hz, 2 H) 7.75 (d, J=8.68 Hz, 1 H) 7.89 (d, J=8.68 Hz, 1 H)

- 15 The diastereo-pure final intermediates were obtained by chromatographic separation on chiral column.

**STEP 6 : Preparation of EXAMPLE 3**

- 20 Using General Procedure 12 starting from ethyl [(2*R*,8*R*)-2,4,31-trimethyl-27,27-dioxo-21,26-dioxa-27 $\lambda^6$ -thia-1,14,15,16-tetraazahexacyclo[20.5.3.1<sup>3,7</sup>.1<sup>9,13</sup>.0<sup>12,16</sup>.0<sup>25,29</sup>]dotriaconta-3(32),4,6,9(31),10,12,14,22,24,29-decaen-8-yl]acetate (1 eq.) or ethyl [(2*R*,8*S*)-2,4,31-trimethyl-27,27-dioxo-21,26-dioxa-27 $\lambda^6$ -thia-1,14,15,16-tetraazahexacyclo  
 [20.5.3.1<sup>3,7</sup>.1<sup>9,13</sup>.0<sup>12,16</sup>.0<sup>25,29</sup>] dotriaconta-3(32),4,6,9(31),10,12,14,22,24,29-decaen-8-yl]acetate  
 25 (1 eq.) as reactants, the title compounds (34% - 78% yields respectively) were obtained.

**Example 3a (2*R*,8*R*)**

**HRMS** calculated for C<sub>30</sub>H<sub>32</sub>N<sub>4</sub>O<sub>6</sub>S: 576.2042; [M+H]<sup>+</sup> found: 577.2119 ( $\delta$ =0.6 ppm)

- <sup>1</sup>**H-NMR** (400 MHz, DMSO-d<sub>6</sub>)  $\delta$  ppm: 12.21 (m, 1 H), 7.7 (d, 1 H), 7.43 (d, 1 H), 7.3 (d, 1 H), 7.1 (d, 1 H), 6.9 (d, 1 H), 6.7 (m, 2 H), 5.89 (m, 1 H), 5.21 (q, 1 H), 4.9 (t, 1 H), 4.73 (m, 2  
 30 H)

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H), 4.05/3.48 (m, 2 H), 3.7 (m, 2 H), 3.25/2.89 (dd, 2 H), 2.8 (s, 3 H), 2.3 (s, 3 H), 2.2/2 (2m, 2 H), 1.61/1.29 (2m, 2 H), 1.1 (d, 3 H)

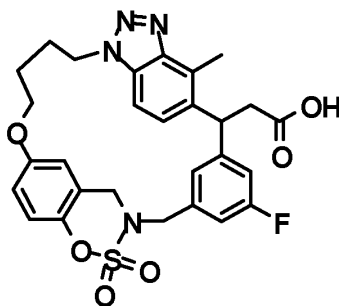
**Example 3b (2R,8S)**

5 **HRMS** calculated for  $C_{30}H_{32}N_4O_6S$ : 576.2042;  $[M+H]^+$  found: 577.2118 ( $\delta=0.5$  ppm)

**$^1H$ -NMR** (400 MHz, DMSO- $d_6$ )  $\delta$  ppm: 12.5-11.8 (m, 1 H), 7.88 (d, 1 H), 7.73 (d, 1 H), 7.43 (d, 1 H), 7.2 (d, 1 H), 7.11 (d, 1 H), 6.93 (d, 1 H), 6.78 (dd, 1 H), 5.69 (d, 1 H), 5.25 (q, 1 H), 4.82-4.67 (m, 2 H), 4.78 (t, 1 H), 4.01/3.4 (m, 2 H), 3.68/3.47 (m, 2 H), 3.19/2.99 (2dd, 2 H), 2.62 (s, 3 H), 2.29 (s, 3 H), 2.23-2 (2m, 2 H), 1.92-1.68 (2m, 2 H), 1.23 (d, 3 H)

10

**EXAMPLE 4** : [5-Fluoro-31-methyl-27,27-dioxo-21,26-dioxa-27 $\lambda^6$ -thia-1,14,15,16-tetraazahexacyclo[20.5.3.1<sup>3,7</sup>.1<sup>9,13</sup>.0<sup>12,16</sup>.0<sup>25,29</sup>]dotriacont-3(32),4,6,9(31),10,12,14,22,24,29-decaen-8-yl]acetic acid



15 **STEP 1 : Preparation of ethyl 3-[3-fluoro-5-(hydroxymethyl)phenyl]-3-(1-{4-[(4-methoxyphenyl)methoxy]butyl}-4-methyl-1*H*-benzotriazol-5-yl)propanoate**

Using General Procedure 6 starting from ethyl (2*E*)-3-(1-{4-[(4-methoxyphenyl)methoxy]butyl}-4-methyl-1*H*-benzotriazol-5-yl)prop-2-enoate (1 eq.) and [3-fluoro-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]methanol (1.5 eq.) as reactants,  
20 the title compound (yellow oil, 30% yield) was obtained.

**$^1H$ -NMR** (400 MHz, DMSO- $d_6$ )  $\delta$  ppm: 7.6 (d, 1 H), 7.5 (d, 1 H), 7.2 (d, 2 H), 7.1-6.9 (m, 3 H), 6.88 (d, 2 H), 5.22 (t, 1 H), 4.85 (t, 1 H), 4.62 (t, 2 H), 4.41 (d, 2 H), 4.3 (s, 2 H), 3.95 (q, 2 H), 3.71 (s, 3 H), 3.39 (t, 2 H), 3.18 (m, 2 H), 2.78 (s, 3 H), 1.9 (m, 2 H), 1.5 (m, 2 H), 1 (t, 3 H)

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**STEP 2 : Preparation of ethyl 3-(3-{[6-(benzyloxy)-2,2-dioxo-2*H*-1,2λ<sup>6</sup>,3-benzoxathiazin-3(4*H*)-yl]methyl}-5-fluorophenyl)-3-(1-{4-[(4-methoxyphenyl)methoxy]butyl}-4-methyl-1*H*-benzotriazol-5-yl)propanoate**

5

Using General Procedure 7 starting from ethyl 3-[3-fluoro-5-(hydroxymethyl)phenyl]-3-(1-{4-[(4-methoxyphenyl)methoxy]butyl}-4-methyl-1*H*-benzotriazol-5-yl)propanoate (1 eq.) and 6-(benzyloxy)-3,4-dihydro-2*H*-1,2λ<sup>6</sup>,3-benzoxathiazine-2,2-dione (1.1 eq.) as reactants, the title compound (64% yield) was obtained.

10 **<sup>1</sup>H-NMR** (400 MHz, DMSO-d<sub>6</sub>) δ ppm: 7.6 (d, 1 H), 7.48 (d, 1 H), 7.4-7.3 (m, 5 H), 7.2-7 (m, 3 H), 7.18 (d, 2 H), 7-6.9 (m, 3 H), 6.85 (d, 2 H), 5.05 (s, 2 H), 4.87 (t, 1 H), 4.62 (s+t, 4 H), 4.3 (s, 4 H), 3.92 (q, 2 H), 3.71 (s, 3 H), 3.38 (t, 2 H), 3.18 (d, 2 H), 2.78 (s, 3 H), 1.92 (m, 2 H), 1.5 (m, 2 H), 1 (t, 3 H)

15 **STEP 3 : Preparation of ethyl 3-{3-fluoro-5-[(6-hydroxy-2,2-dioxo-2*H*-1,2λ<sup>6</sup>,3-benzoxathiazin-3(4*H*)-yl)methyl]phenyl}-3-[1-(4-hydroxybutyl)-4-methyl-1*H*-benzotriazol-5-yl]propanoate**

Using General Procedure 8 starting from ethyl 3-(3-{[6-(benzyloxy)-2,2-dioxo-2*H*-1,2λ<sup>6</sup>,3-benzoxathiazin-3(4*H*)-yl]methyl}-5-fluorophenyl)-3-(1-{4-[(4-methoxyphenyl)methoxy]butyl}-4-methyl-1*H*-benzotriazol-5-yl)propanoate (1 eq.) as a reactant, the title compound (96% yield) was obtained.

20 **<sup>1</sup>H-NMR** (400 MHz, DMSO-d<sub>6</sub>) δ ppm: 9.6/4.4 (s+t, 2 H), 7.62 (d, 1 H), 7.5 (d, 1 H), 7.21 (d, 1 H), 7.1 (dd, 1 H), 7.02 (dd, 1 H), 6.81 (d, 1 H), 6.7 (dd, 1 H), 6.6 (d, 1 H), 4.85 (t, 1 H), 4.65 (t, 2 H), 4.52 (s, 2 H), 4.29 (s, 2 H), 3.95 (q, 2 H), 3.4 (q, 2 H), 3.2 (d, 2 H), 2.79 (s, 3 H), 1.9 (m, 2 H), 1.38 (m, 2 H), 1 (t, 3 H)

**STEP 4 : Preparation of ethyl 3-[1-(4-bromobutyl)-4-methyl-1*H*-benzotriazol-5-yl]-3-{3-fluoro-5-[(6-hydroxy-2,2-dioxo-2*H*-1,2λ<sup>6</sup>,3-benzoxathiazin-3(4*H*)-yl)methyl]phenyl}propanoate**

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Using General Procedure 9 starting from ethyl 3-{3-fluoro-5-[(6-hydroxy-2,2-dioxo-2*H*-1,2λ<sup>6</sup>,3-benzoxathiazin-3(4*H*)-yl)methyl]phenyl}-3-[1-(4-hydroxybutyl)-4-methyl-1*H*-benzotriazol-5-yl]propanoate (1 eq.) as a reactant, the title compound (66% yield) was obtained.

- 5 <sup>1</sup>H-NMR (400 MHz, DMSO-d<sub>6</sub>) δ ppm: 9.6 (s, 1 H), 7.64 (d, 1 H), 7.51 (d, 1 H), 7.2 (t, 1 H), 7.13/7 (2dt, 2 H), 6.88 (d, 1 H), 6.7 (dd, 1 H), 6.59 (d, 1 H), 4.87 (t, 1 H), 4.69 (t, 2 H), 4.57 (s, 2 H), 4.29 (s, 2 H), 3.92 (q, 2 H), 3.52 (t, 2 H), 3.19 (d, 2 H), 2.78 (s, 3 H), 1.99 (m, 2 H), 1.78 (m, 2 H), 1 (t, 3 H)

- 10 **STEP 5: Preparation of ethyl [5-fluoro-31-methyl-27,27-dioxo-21,26-dioxo-27λ<sup>6</sup>-thia-1,14,15,16-tetraazahexacyclo[20.5.3.1<sup>3,7</sup>.1<sup>9,13</sup>.0<sup>12,16</sup>.0<sup>25,29</sup>]dotriaconta-3(32),4,6,9(31),10,12,14,22,24,29-decaen-8-yl]acetate**

Using General Procedure 11 starting from ethyl 3-[1-(4-bromobutyl)-4-methyl-1*H*-benzotriazol-5-yl]-3-{3-fluoro-5-[(6-hydroxy-2,2-dioxo-2*H*-1,2λ<sup>6</sup>,3-benzoxathiazin-3(4*H*)-yl)methyl]phenyl} propanoate (1 eq.) as a reactant, the title compound (white solid, 72% yield) was obtained.

- 15 <sup>1</sup>H-NMR (400 MHz, DMSO-d<sub>6</sub>) δ ppm: 7.59 (d, 1 H), 7.4/7.06 (2m, 2 H), 7.32 (d, 1 H), 6.91 (d, 1 H), 6.74 (m, 1 H), 6.69 (dd, 1 H), 6 (d, 1 H), 4.87-4.67 (m, 3 H), 4.15/4.05 (2dd, 4 H),  
20 3.93 (m, 2 H), 3.67/3.37 (2m, 2 H), 3.27/3.11 (2m, 2 H), 2.75 (s, 3 H), 2.18/1.96 (2m, 2 H), 1.68/1.45 (2m, 2 H), 1.01 (t, 3 H)

#### **STEP 6: Preparation of EXAMPLE 4**

- 25 Using General Procedure 12 starting from ethyl [5-fluoro-31-methyl-27,27-dioxo-21,26-dioxo-27λ<sup>6</sup>-thia-1,14,15,16-tetraazahexacyclo[20.5.3.1<sup>3,7</sup>.1<sup>9,13</sup>.0<sup>12,16</sup>.0<sup>25,29</sup>]dotriaconta-3(32),4,6,9(31),10,12,14,22,24,29-decaen-8-yl]acetate (1 eq.) as a reactant, the title compound (white solid, 98% yield) was obtained.

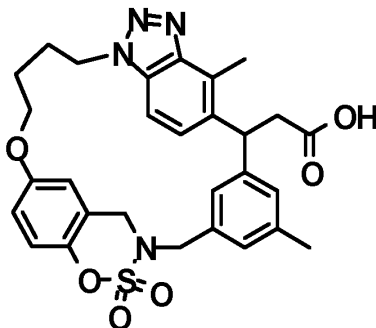
**HRMS** calculated for C<sub>28</sub>H<sub>27</sub>FN<sub>4</sub>O<sub>6</sub>S: 566.1635; [M+H]<sup>+</sup>found: 567.1710 (δ=0.3 ppm)

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<sup>1</sup>H-NMR (400 MHz, DMSO-d<sub>6</sub>) δ ppm: 12.19 (m, 1 H), 7.59 (d, 1 H), 7.4/7.06 (2m, 2 H), 7.3 (d, 1 H), 6.91 (d, 1 H), 6.71 (m, 1 H), 6.69 (dd, 1 H), 6 (d, 1 H), 4.87-4.67 (m, 3 H), 4.14/4.04 (2dd, 4 H), 3.68/3.38 (2m, 2 H), 3.17/2.91 (2m, 2 H), 2.75 (s, 3 H), 2.19/1.97 (2m, 2 H), 1.69/1.46 (2m, 2 H)

5

**EXAMPLE 5 :** [5,31-Dimethyl-27,27-dioxo-21,26-dioxa-27λ<sup>6</sup>-thia-1,14,15,16-tetraazahexacyclo[20.5.3.1<sup>3,7</sup>.1<sup>9,13</sup>.0<sup>12,16</sup>.0<sup>25,29</sup>]dotriaconta-3(32),4,6,9(31),10,12,14,22,24,29-decaen-8-yl]acetic acid



10

**STEP B1 : Preparation of [3-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]methanol**

Using General Procedure 3 starting from (3-bromo-5-methylphenyl)methanol (1 eq., 2.01 g, 10 mmol) as a reactant, the title compound (1.13 g, 45% yield) was obtained.

15

<sup>1</sup>H-NMR (400 MHz, DMSO-d<sub>6</sub>) δ ppm: 7.44/7.35/7.23 (3tf, 3 H), 5.12 (t, 1 H), 4.46 (d, 2 H), 2.29 (s, 3 H), 1.28 (s, 12 H)

20

**STEP 1 : Preparation of ethyl 3-[3-(hydroxymethyl)-5-methylphenyl]-3-(1-{4-[(4-methoxyphenyl)methoxy]butyl}-4-methyl-1H-benzotriazol-5-yl)propanoate**

Using General Procedure 6 starting from ethyl (2E)-3-(1-{4-[(4-methoxyphenyl)methoxy]butyl}-4-methyl-1H-benzotriazol-5-yl)prop-2-enoate (1 eq.) and [3-

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methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]methanol (2 eq.) as reactants, the title compound (68% yield) was obtained.

<sup>1</sup>H-NMR (400 MHz, DMSO-d<sub>6</sub>) δ ppm: 7.58 (d, 1 H), 7.47 (d, 1 H), 7.2 (d, 2 H), 7.04/7/6.93 (3sl, 3 H), 6.87 (d, 2 H), 5.05 (t, 1 H), 4.82 (t, 1 H), 4.64 (t, 2 H), 4.39 (d, 2 H), 4.32 (s, 2 H), 3.92 (qd, 2 H), 3.73 (s, 3 H), 3.38 (t, 2 H), 3.13 (m, 2 H), 2.76 (s, 3 H), 2.23 (s, 3 H), 1.92 (m, 2 H), 1.48 (m, 2 H), 0.99 (t, 3 H)

**STEP 2 : Preparation of ethyl 3-(3-{[6-(benzyloxy)-2,2-dioxo-2H-1,2λ<sup>6</sup>,3-benzoxathiazin-3(4H)-yl]methyl}-5-methylphenyl)-3-(1-{4-[(4-methoxyphenyl)methoxy]butyl}-4-methyl-1H-benzotriazol-5-yl)propanoate**

Using General Procedure 7 starting from ethyl 3-[3-(hydroxymethyl)-5-methylphenyl]-3-(1-{4-[(4-methoxyphenyl)methoxy]butyl}-4-methyl-1H-benzotriazol-5-yl)propanoate (1 eq.) and 6-(benzyloxy)-3,4-dihydro-2H-1,2λ<sup>6</sup>,3-benzoxathiazine-2,2-dione (1.5 eq.) as reactants the title compound (86% yield) was obtained.

<sup>1</sup>H-NMR (400 MHz, DMSO-d<sub>6</sub>) δ ppm: 7.57 (d, 1 H), 7.45-7.3 (m, 5 H), 7.45 (d, 1 H), 7.18 (d, 2 H), 7.14/7.07/6.98 (3tf, 3 H), 7.03/7/6.94 (dd+d+d, 3 H), 6.86 (d, 2 H), 5.05 (s, 2 H), 4.82 (t, 1 H), 4.63 (t, 2 H), 4.55 (s, 2 H), 4.31 (s, 2 H), 4.23 (s, 2 H), 3.92 (q, 2 H), 3.73 (s, 3 H), 3.36 (t, 2 H), 3.12 (d, 2 H), 2.76 (s, 3 H), 2.22 (s, 3 H), 1.91 (m, 2 H), 1.47 (m, 2 H), 0.98 (t, 3 H)

**STEP 3 : Preparation of ethyl 3-[1-(4-hydroxybutyl)-4-methyl-1H-benzotriazol-5-yl]-3-{3-[(6-hydroxy-2,2-dioxo-2H-1,2λ<sup>6</sup>,3-benzoxathiazin-3(4H)-yl)methyl]-5-methylphenyl}propanoate**

Using General Procedure 8 starting from ethyl 3-(3-{[6-(benzyloxy)-2,2-dioxo-2H-1,2λ<sup>6</sup>,3-benzoxathiazin-3(4H)-yl]methyl}-5-methylphenyl)-3-(1-{4-[(4-methoxyphenyl)methoxy]butyl}-4-methyl-1H-benzotriazol-5-yl)propanoate (1 eq.) as a reactant, the title compound (99% yield) was obtained.

<sup>1</sup>H-NMR (400 MHz, DMSO-d<sub>6</sub>) δ ppm: 9.63 (m, 1 H), 7.62 (d, 1 H), 7.47 (d, 1 H), 7.15/7.08/6.99 (3tf, 3 H), 6.91 (d, 1 H), 6.73 (dd, 1 H), 6.6 (d, 1 H), 4.83 (t, 1 H), 4.65 (t, 2 H),



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4.5/4.22 (2s, 4 H), 3.94 (q, 2 H), 3.39 (t, 2 H), 3.14 (d, 2 H), 2.77 (s, 3 H), 2.24 (s, 3 H), 1.91 (m, 2 H), 1.37 (m, 2 H), 1 (t, 3 H)

**STEP 4 : Preparation of ethyl 3-[1-(4-bromobutyl)-4-methyl-1*H*-benzotriazol-5-yl]-3-{3-  
5 [(6-hydroxy-2,2-dioxo-2*H*-1,2λ<sup>6</sup>,3-benzoxathiazin-3(4*H*)-yl)methyl]-5-  
methylphenyl}propanoate**

Using General Procedure 9 starting from ethyl 3-[1-(4-hydroxybutyl)-4-methyl-1*H*-  
benzotriazol-5-yl]-3-{3-[(6-hydroxy-2,2-dioxo-2*H*-1,2λ<sup>6</sup>,3-benzoxathiazin-3(4*H*)-yl)methyl]-  
10 5-methylphenyl} propanoate (1 eq.) as a reactant, the title compound (78% yield) was obtained.  
**<sup>1</sup>H-NMR** (400 MHz, DMSO-d<sub>6</sub>) δ ppm: 9.61 (m, 1 H), 7.63 (d, 1 H), 7.49 (d, 1 H),  
7.14/7.07/6.98 (3tf, 3 H), 6.9 (d, 1 H), 6.73 (dd, 1 H), 6.59 (d, 1 H), 4.82 (t, 1 H), 4.69 (t, 2 H),  
4.49/4.2 (2s, 4 H), 3.93 (q, 2 H), 3.54 (t, 2 H), 3.14 (d, 2 H), 2.76 (s, 3 H), 2.22 (s, 3 H), 1.99  
(m, 2 H), 1.77 (m, 2 H), 0.99 (t, 3 H)

**STEP 5 : Preparation of ethyl [5,31-dimethyl-27,27-dioxo-21,26-dioxa-27λ<sup>6</sup>-thia-  
1,14,15,16-tetraazahexacyclo[20.5.3.1<sup>3,7</sup>.1<sup>9,13</sup>.0<sup>12,16</sup>.0<sup>25,29</sup>]dotriaconta-  
3(32),4,6,9(31),10,12,14,22,24,29-decaen-8-yl]acetate**

Using General Procedure 11 starting from ethyl 3-[1-(4-bromobutyl)-4-methyl-1*H*-  
benzotriazol-5-yl]-3-{3-[(6-hydroxy-2,2-dioxo-2*H*-1,2λ<sup>6</sup>,3-benzoxathiazin-3(4*H*)-yl)methyl]-  
5-methylphenyl} propanoate (1 eq.) as a reactant, the title compound (98% yield) was obtained.  
**<sup>1</sup>H-NMR** (400 MHz, DMSO-d<sub>6</sub>) δ ppm: 7.6 (d, 1 H), 7.35 (d, 1 H), 7.34/7.09/6.58 (3m, 3 H),  
6.93 (d, 1 H), 6.73 (dd, 1 H), 5.98 (d, 1 H), 4.84-4.66 (2m, 3 H), 4.03/3.98 (2s, 4 H), 3.93 (m, 2  
25 H), 3.68/3.45 (2m, 2 H), 3.21/3.09 (2m, 2 H), 2.71 (s, 3 H), 2.36 (s, 3 H), 2.19/1.99 (2m, 2 H),  
1.68/1.48 (2m, 2 H), 1.01 (t, 3 H)

**STEP 6 : Preparation of EXAMPLE 5**

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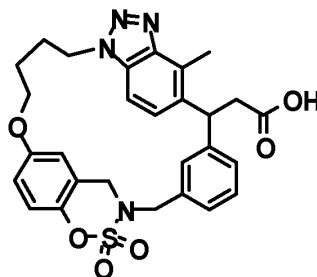
Using General Procedure 12 starting from ethyl [5,31-dimethyl-27,27-dioxo-21,26-dioxa-27 $\lambda^6$ -thia-1,14,15,16-tetraazahexacyclo[20.5.3.1<sup>3,7</sup>.1<sup>9,13</sup>.0<sup>12,16</sup>.0<sup>25,29</sup>]dotriaconta-3(32),4,6,9(31),10,12,14,22,24,29-decaen-8-yl]acetate (1 eq.) as a reactant, the title compound (white solid, 50% yield) was obtained.

5 **HRMS** calculated for C<sub>29</sub>H<sub>30</sub>N<sub>4</sub>O<sub>6</sub>S: 562.1886; [M+H]<sup>+</sup> found: 563.1963 ( $\delta$ =0.7 ppm)

**<sup>1</sup>H-NMR** (400 MHz, DMSO-d<sub>6</sub>)  $\delta$  ppm: 12.15 (m, 1 H), 7.6 (d, 1 H), 7.34/7.09/6.57 (3sl, 3 H), 7.33 (d, 1 H), 6.94 (d, 1 H), 6.73 (dd, 1 H), 5.98 (d, 1 H), 4.85-4.67 (2m, 3 H), 4.03/3.98 (2s, 4 H), 3.68/3.45 (2m, 2 H), 3.11/2.97 (2m, 2 H), 2.71 (s, 3 H), 2.36 (s, 3 H), 2.19/1.99 (2m, 2 H), 1.71/1.47 (2m, 2 H)

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**EXAMPLE 6 :** [31-Methyl-27,27-dioxo-21,26-dioxa-27 $\lambda^6$ -thia-1,14,15,16-tetraazahexacyclo[20.5.3.1<sup>3,7</sup>.1<sup>9,13</sup>.0<sup>12,16</sup>.0<sup>25,29</sup>]dotriaconta-3(32),4,6,9(31),10,12,14,22,24,29-decaen-8-yl]acetic acid



15 **STEP 1 :** Preparation of ethyl 3-[3-(hydroxymethyl)phenyl]-3-(1-{4-[(4-methoxyphenyl)methoxy]butyl}-4-methyl-1H-benzotriazol-5-yl)propanoate

Using General Procedure 6 starting from ethyl (2E)-3-(1-{4-[(4-methoxyphenyl)methoxy]butyl}-4-methyl-1H-benzotriazol-5-yl)prop-2-enoate (1 eq.) and [3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]methanol (2 eq.) as reactants the title compound (75% yield) was obtained.

20 **<sup>1</sup>H-NMR** (400 MHz, DMSO-d<sub>6</sub>)  $\delta$  ppm: 7.58 (d, 1 H), 7.48 (d, 1 H), 7.26-7.1 (m, 4 H), 7.2 (d, 2 H), 6.88 (d, 2 H), 5.09 (t, 1 H), 4.86 (t, 1 H), 4.64 (t, 2 H), 4.42 (d, 2 H), 4.32 (s, 2 H), 3.92

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(q, 2 H), 3.73 (s, 3 H), 3.38 (t, 2 H), 3.18/3.13 (2dd, 2 H), 2.77 (s, 3 H), 1.92 (m, 2 H), 1.48 (m, 2 H), 0.99 (t, 3 H)

**STEP 2 : Preparation of ethyl 3-[1-(4-hydroxybutyl)-4-methyl-1*H*-benzotriazol-5-yl]-3-{3-[(6-hydroxy-2,2-dioxo-2*H*-1,2λ<sup>6</sup>,3-benzoxathiazin-3(4*H*)-yl)methyl]phenyl}propanoate**

Using General Procedure 7 starting from ethyl 3-[3-(hydroxymethyl)phenyl]-3-(1-{4-[(4-methoxyphenyl)methoxy]butyl}-4-methyl-1*H*-benzotriazol-5-yl)propanoate (1 eq.) and 6-benzyloxy)-3,4-dihydro-2*H*-1,2λ<sup>6</sup>,3-benzoxathiazine-2,2-dione (1.5 eq.) as reactants ethyl 3-(3-{[6-(benzyloxy)-2,2-dioxo-2*H*-1,2λ<sup>6</sup>,3-benzoxathiazin-3(4*H*)-yl)methyl]phenyl}-3-(1-{4-[(4-methoxyphenyl)methoxy]butyl}-4-methyl-1*H*-benzotriazol-5-yl)propanoate was obtained. The crude product was used without further purification using General Procedure 8. The title compound was obtained (77% yield).

**<sup>1</sup>H-NMR** (400 MHz, DMSO-d<sub>6</sub>) δ ppm: 9.61 (m, 1 H), 7.61 (d, 1 H), 7.48 (d, 1 H), 7.36 (m, 1 H), 7.28-7.14 (m, 3 H), 6.89 (d, 1 H), 6.72 (dd, 1 H), 6.59 (d, 1 H), 4.86 (t, 1 H), 4.65 (t, 2 H), 4.51/4.26 (2s, 4 H), 4.41 (t, 2 H), 3.93 (q, 2 H), 3.38 (q, 2 H), 3.16 (d, 2 H), 2.76 (s, 3 H), 1.9 (m, 2 H), 1.37 (m, 2 H), 1 (t, 3 H)

**STEP 3 : Preparation of ethyl 3-[1-(4-bromobutyl)-4-methyl-1*H*-benzotriazol-5-yl]-3-{3-[(6-hydroxy-2,2-dioxo-2*H*-1,2λ<sup>6</sup>,3-benzoxathiazin-3(4*H*)-yl)methyl]phenyl}propanoate**

Using General Procedure 9 starting from ethyl 3-[1-(4-hydroxybutyl)-4-methyl-1*H*-benzotriazol-5-yl]-3-{3-[(6-hydroxy-2,2-dioxo-2*H*-1,2λ<sup>6</sup>,3-benzoxathiazin-3(4*H*)-yl)methyl]phenyl} propanoate (1 eq.) as a reactant, the title compound (99% yield) was obtained.

**<sup>1</sup>H-NMR** (400 MHz, DMSO-d<sub>6</sub>) δ ppm: 9.61 (m, 1 H), 7.61 (d, 1 H), 7.49 (d, 1 H), 7.25-7.14 (m, 3 H), 7.22 (m, 1 H), 6.89 (d, 1 H), 6.72 (dd, 1 H), 6.59 (d, 1 H), 4.88 (t, 1 H), 4.7 (t, 2 H),

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4.5/4.26 (2s, 4 H), 3.91 (q, 2 H), 3.52 (t, 2 H), 3.16 (d, 2 H), 2.76 (s, 3 H), 2 (m, 2 H), 1.78 (m, 2 H), 1 (t, 3 H)

**STEP 4 : Preparation of ethyl [31-methyl-27,27-dioxo-21,26-dioxa-27 $\lambda^6$ -thia-1,14,15,16-tetraazahexacyclo[20.5.3.1<sup>3,7</sup>.1<sup>9,13</sup>.0<sup>12,16</sup>.0<sup>25,29</sup>]dotriaconta-3(32),4,6,9(31),10,12,14,22,24,29-decaen-8-yl]acetate**

Using General Procedure 11 starting from ethyl 3-[1-(4-bromobutyl)-4-methyl-1*H*-benzotriazol-5-yl]-3-{3-[(6-hydroxy-2,2-dioxo-2*H*-1,2 $\lambda^6$ ,3-benzoxathiazin-3(4*H*)-yl)methyl]phenyl} propanoate (1 eq.) as a reactant, the title compound (78% yield) was obtained.

**<sup>1</sup>H-NMR** (400 MHz, DMSO-d<sub>6</sub>)  $\delta$  ppm: 7.6 (d, 1 H), 7.5 (d, 1 H), 7.4 (t, 1 H), 7.31 (d, 1 H), 7.25 (d, 1 H), 6.95 (d, 1 H), 6.81 (sl, 1 H), 6.7 (dd, 1 H), 6 (d, 1 H), 4.8/4.71 (2m, 2 H), 4.8 (m, 1 H), 4.11/4 (2s, 4 H), 3.92 (q, 2 H), 3.7/3.4 (2m, 2 H), 3.2/3.1 (2dd, 2 H), 2.71 (s, 3 H), 2.2/2 (2m, 2 H), 1.7/1.5 (2m, 2 H), 1 (t, 3 H)

**STEP 5 : Preparation of EXAMPLE 6**

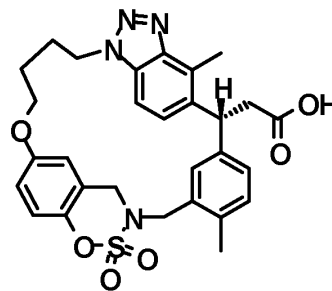
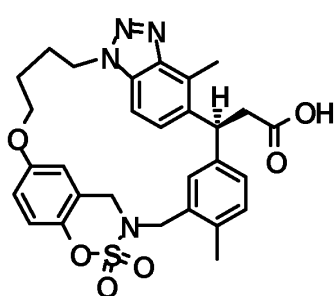
Using General Procedure 12 starting from ethyl [31-methyl-27,27-dioxo-21,26-dioxa-27 $\lambda^6$ -thia-1,14,15,16-tetraazahexacyclo[20.5.3.1<sup>3,7</sup>.1<sup>9,13</sup>.0<sup>12,16</sup>.0<sup>25,29</sup>]dotriaconta-3(32),4,6,9(31),10,12,14,22,24,29-decaen-8-yl]acetate (1 eq.) as a reactant, the title compound (white solid, 21% yield) was obtained.

**HRMS** calculated for C<sub>28</sub>H<sub>28</sub>N<sub>4</sub>O<sub>6</sub>S: 548.1730; [M+H]<sup>+</sup> found: 549.1809 ( $\delta$ =1.2 ppm)

**<sup>1</sup>H-NMR** (400 MHz, DMSO-d<sub>6</sub>)  $\delta$  ppm: 7.58 (d, 1 H), 7.5 (d, 1 H), 7.41 (t, 1 H), 7.32 (d, 1 H), 7.26 (d, 1 H), 6.92 (d, 1 H), 6.8 (sl, 1 H), 6.72 (dd, 1 H), 5.98 (d, 1 H), 4.8/4.72 (2m, 2 H), 4.8 (m, 1 H), 4.1 (s, 2 H), 4 (s, 2 H), 3.68/3.4 (2m, 2 H), 3.12/3 (2dd, 2 H), 2.7 (s, 3 H), 2.2/1.98 (2m, 2 H), 1.7/1.48 (2m, 2 H)

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**EXAMPLE 7 :** [(8*S*)-4,31-Dimethyl-27,27-dioxo-21,26-dioxa-27 $\lambda^6$ -thia-1,14,15,16-tetraazahexacyclo[20.5.3.1<sup>3,7</sup>.1<sup>9,13</sup>.0<sup>12,16</sup>.0<sup>25,29</sup>]dotriaconta-3(32),4,6,9(31),10,12,14,22,24,29-decaen-8-yl]acetic acid and [(8*R*)-4,31-dimethyl-27,27-dioxo-21,26-dioxa-27 $\lambda^6$ -thia-1,14,15,16-tetraazahexacyclo[20.5.3.1<sup>3,7</sup>.1<sup>9,13</sup>.0<sup>12,16</sup>.0<sup>25,29</sup>]dotriaconta-3(32),4,6,9(31),10,12,14,22,24,29-decaen-8-yl]acetic acid



**STEP A1 : Preparation of *N*-[4-(benzyloxy)butyl]-4-bromo-3-methyl-2-nitroaniline**

The mixture of 4-bromo-3-methyl-2-nitro-aniline (1 eq., 10 g, 43 mmol), NaOH (1.2 eq., 2.1 g, 52 mmol) and acetone (2 mL/mmol, 87 mL) was heated to 65 °C in 15 min. 4-Bromobutoxymethylbenzene (1.2 eq.) was added to the mixture over a period of 5 min. The mixture was stirred at 65°C for 72 h. After completion of the reaction, the mixture was quenched with 400 mL water. The mixture was extracted with 3x150 ml EtOAc. The organic layer was dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>, filtered, concentrated to dryness to give the crude product, which was purified by normal phase silica gel chromatography using heptane-DCM (20:80) as an eluent to give the title compound (6.5 g, orange oil, 38% yield).

<sup>1</sup>H-NMR (400 MHz, DMSO-d<sub>6</sub>) δ ppm: 7.5 (d, 1 H), 7.3 (m, 5 H), 6.7 (d, 1 H), 6.15 (t, 1 H), 4.4 (s, 2 H), 3.45 (t, 2 H), 3.1 (q, 2 H), 2.2 (s, 3 H), 1.6 (m, 4 H)

**STEP A2 : Preparation of *N*<sup>1</sup>-[4-(benzyloxy)butyl]-4-bromo-3-methylbenzene-1,2-diamine**

To a solution of *N*-[4-(benzyloxy)butyl]-4-bromo-3-methyl-2-nitroaniline (1 eq., 6.1 g, 16

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mmol) in EtOH (4 mL/mmol, 62 mL) tin(II) dichloride dihydrate (4 eq., 13 g, 62 mmol) was added at RT. The reaction mixture was heated to 70 °C and stirred at this temperature for 3 h. After completion of the reaction 5N aq. NaOH solution (40 mL), then 160 ml EtOAc were added. The mixture was filtered, the mother liquor was separated. The organic layer was dried  
5 over anhydrous Na<sub>2</sub>SO<sub>4</sub>, filtered, concentrated to dryness to give the crude product, which was purified by reversed-phase chromatography using water-MeCN as an eluent (4 g, 71% yield).  
<sup>1</sup>H-NMR (400 MHz, DMSO-d<sub>6</sub>) δ ppm: 7.35-7.25 (m, 5 H), 6.7 (d, 1 H), 6.22 (d, 1 H), 4.6 (s, 2 H), 4.52 (t, 1 H), 4.42 (s, 2 H), 3.49 (t, 2 H), 3 (q, 2 H), 2.15 (s, 3 H), 1.65 (m, 4 H)

10 **STEP A3 : Preparation of 1-[4-(benzyloxy)butyl]-5-bromo-4-methyl-1H-benzotriazole**

Using General Procedure 2 STEP 4 starting from N<sup>1</sup>-[4-(benzyloxy)butyl]-4-bromo-3-methylbenzene-1,2-diamine (1 eq.) as a reactant, the title compound (orange oil, 79% yield) was obtained.

15 <sup>1</sup>H-NMR (400 MHz, DMSO-d<sub>6</sub>) δ ppm: 7.68 (s, 2 H), 7.3-7.2 (m, 5 H), 4.7 (t, 2 H), 4.4 (s, 2 H), 3.42 (t, 2 H), 2.7 (s, 3 H), 1.98 (m, 2 H), 1.5 (m, 2 H)

**STEP A4 : Preparation of ethyl (2E)-3-{1-[4-(benzyloxy)butyl]-4-methyl-1H-benzotriazol-5-yl}prop-2-enoate**

20

Using General Procedure 2 STEP 5 starting from 1-[4-(benzyloxy)butyl]-5-bromo-4-methyl-1H-benzotriazole (1 eq.) as a reactant, the title compound (black oil, 96% yield) was obtained.

<sup>1</sup>H-NMR (400 MHz, DMSO-d<sub>6</sub>) δ ppm: 8 (d, 1 H), 7.9 (d, 1 H), 7.7 (d, 1 H), 7.35-7.2 (m, 5 H), 6.65 (d, 1 H), 4.72 (t, 2 H), 4.4 (s, 2 H), 4.2 (q, 2 H), 3.45 (t, 2 H), 2.8 (s, 3 H), 1.95 (quint, 2  
25 H), 1.52 (quint, 2 H), 1.3 (t, 3 H)

**STEP 1 : Preparation of ethyl 3-{1-[4-(benzyloxy)butyl]-4-methyl-1H-benzotriazol-5-yl}-3-[3-(hydroxymethyl)-4-methylphenyl]propanoate**

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Using General Procedure 6 starting from ethyl (2*E*)-3-{1-[4-(benzyloxy)butyl]-4-methyl-1*H*-benzotriazol-5-yl}prop-2-enoate (1 eq.) and [2-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]methanol (1.5 eq.) as reactants the title compound (49% yield) was obtained.

5 <sup>1</sup>H-NMR (400 MHz, DMSO-d<sub>6</sub>) δ ppm: 7.6 (d, 1 H), 7.45 (d, 1 H), 7.35-7.2 (m, 6 H), 7.1 (dd, 1 H), 7.01 (d, 1 H), 4.99 (t, 1 H), 4.82 (t, 1 H), 4.65 (t, 2 H), 4.4 (d+s, 4 H), 3.91 (q, 2 H), 3.45 (t, 2 H), 3.15 (d, 2 H), 2.75 (s, 3 H), 2.15 (s, 3 H), 1.95 (m, 2 H), 1.5 (m, 2 H), 1 (t, 3 H)

10 **STEP 2 : Preparation of ethyl 3-{1-[4-(benzyloxy)butyl]-4-methyl-1*H*-benzotriazol-5-yl}-3-{[6-(benzyloxy)-2,2-dioxo-2*H*-1,2λ<sup>6</sup>,3-benzoxathiazin-3(4*H*)-yl]methyl}-4-methylphenyl}propanoate**

Using General Procedure 7 starting from ethyl 3-{1-[4-(benzyloxy)butyl]-4-methyl-1*H*-benzotriazol-5-yl}-3-[3-(hydroxymethyl)-4-methylphenyl]propanoate (1 eq.) and 6-(benzyloxy)-3,4-dihydro-2*H*-1,2λ<sup>6</sup>,3-benzoxathiazine-2,2-dione (2.2 eq.) as reactants the title compound (60% yield) was obtained.

15 <sup>1</sup>H-NMR (400 MHz, DMSO-d<sub>6</sub>) δ ppm: 7.58 (d, 1 H), 7.48 (d, 1 H), 7.45-7.2 (m, 13 H), 7.15 (d, 1 H), 7.05 (dd, 1 H), 6.95 (d, 1 H), 5.1 (s, 2 H), 4.85 (t, 1 H), 4.65 (t, 2 H), 4.45/4.4 (2s, 4 H), 4.22 (s, 2 H), 3.92 (q, 2 H), 3.42 (t, 2 H), 3.15 (m, 2 H), 2.75 (s, 3 H), 2.2 (s, 3 H), 1.92 (m, 20 2 H), 1.48 (m, 2 H), 1.2 (t, 3 H)

**STEP 3 : Preparation of ethyl 3-[1-(4-hydroxybutyl)-4-methyl-1*H*-benzotriazol-5-yl]-3-{3-[(6-hydroxy-2,2-dioxo-2*H*-1,2λ<sup>6</sup>,3-benzoxathiazin-3(4*H*)-yl)methyl]-4-methylphenyl}propanoate**

25

Using General Procedure 8 starting from ethyl 3-{1-[4-(benzyloxy)butyl]-4-methyl-1*H*-benzotriazol-5-yl}-3-(3-{[6-(benzyloxy)-2,2-dioxo-2*H*-1,2λ<sup>6</sup>,3-benzoxathiazin-3(4*H*)-yl]methyl}-4-methylphenyl)propanoate (1 eq.) as a reactant, the title compound (white solid, quant.) was obtained.

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<sup>1</sup>H-NMR (400 MHz, DMSO-d<sub>6</sub>) δ ppm: 7.62 (d, 1 H), 7.5 (d, 1 H), 7.22 (s, 1 H), 7.2 (d, 1 H), 7.15 (d, 1 H), 7 (s, 1 H), 6.8 (dd, 1 H), 6.6 (d, 1 H), 4.85 (t, 1 H), 4.65 (t, 2 H), 4.4 (m, 1 H), 4.4 (s, 2 H), 4.2 (m, 2 H), 3.95 (q, 2 H), 3.38 (tl, 2 H), 3.15 (m, 2 H), 2.75 (s, 3 H), 2.32 (s, 3 H), 1.9 (m, 2 H), 1.35 (m, 2 H), 1 (t, 3 H)

5

**STEP 4 : Preparation of ethyl 3-[1-(4-bromobutyl)-4-methyl-1H-benzotriazol-5-yl]-3-{3-[(6-hydroxy-2,2-dioxo-2H-1,2λ<sup>6</sup>,3-benzoxathiazin-3(4H)-yl)methyl]-4-methylphenyl}propanoate**

10 Using General Procedure 9 starting from ethyl 3-[1-(4-hydroxybutyl)-4-methyl-1H-benzotriazol-5-yl]-3-{3-[(6-hydroxy-2,2-dioxo-2H-1,2λ<sup>6</sup>,3-benzoxathiazin-3(4H)-yl)methyl]-4-methylphenyl} propanoate (1 eq.) as a reactant, the title compound (73% yield) was obtained.

<sup>1</sup>H-NMR (400 MHz, DMSO-d<sub>6</sub>) δ ppm: 9.68 (s, 1 H), 7.63 (d, 1 H), 7.52 (d, 1 H), 7.22 (d, 1 H), 7.2 (dd, 1 H), 7.13 (d, 1 H), 6.99 (d, 1 H), 6.79 (dd, 1 H), 6.6 (d, 1 H), 4.84 (t, 1 H), 4.69 (t, 2 H), 4.38 (s, 2 H), 4.2 (m, 2 H), 3.94 (q, 2 H), 3.54 (t, 2 H), 3.19 (m, 2 H), 2.76 (s, 3 H), 2.22 (s, 3 H), 1.99 (quint, 2 H), 1.77 (quint, 2 H), 1 (t, 3 H)

15

**STEP 5 : Preparation of ethyl [4,31-dimethyl-27,27-dioxo-21,26-dioxa-27λ<sup>6</sup>-thia-1,14,15,16-tetraazahexacyclo[20.5.3.1<sup>3,7</sup>.1<sup>9,13</sup>.0<sup>12,16</sup>.0<sup>25,29</sup>]dotriacont-3(32),4,6,9(31),10,12,14,22,24,29-decaen-8-yl]acetate**

20

Using General Procedure 11 starting from ethyl 3-[1-(4-bromobutyl)-4-methyl-1H-benzotriazol-5-yl]-3-{3-[(6-hydroxy-2,2-dioxo-2H-1,2λ<sup>6</sup>,3-benzoxathiazin-3(4H)-yl)methyl]-4-methylphenyl} propanoate (1 eq.) as a reactant, the title compound (white solid, 79% yield) was obtained.

25

<sup>1</sup>H-NMR (400 MHz, DMSO-d<sub>6</sub>) δ ppm: 7.7 (d, 1 H), 7.5 (dd, 1 H), 7.45 (d, 1 H), 7.3 (d, 1 H), 7 (d, 1 H), 6.8 (dd, 1 H), 6.55 (d, 1 H), 5.85 (d, 1 H), 4.8 (m, 3 H), 4.1/3.95 (m, 2 H), 4/3.8 (m, 2 H), 3.9 (m, 2 H), 3.7/3.45 (m, 2 H), 3.15/3.08 (m, 2 H), 2.63 (s, 3 H), 2.31 (s, 3 H), 2.2/2 (m, 2 H), 1.8/1.6 (m, 2 H), 1.02 (t, 3 H)

30



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**STEP 6 : Preparation of EXAMPLE 7**

Using General Procedure 12 starting from ethyl [4,31-dimethyl-27,27-dioxo-21,26-dioxa-27 $\lambda^6$ -thia-1,14,15,16-tetraazahexacyclo[20.5.3.1<sup>3,7</sup>.1<sup>9,13</sup>.0<sup>12,16</sup>.0<sup>25,29</sup>]dotriaconta-

- 5 3(32),4,6,9(31),10,12,14,22,24,29-decaen-8-yl]acetate (1 eq.) as a reactant, the title compound (white solid, 93% yield) was obtained.

The enantiopure final products or final intermediates were obtained by chromatographic separation on chiral column.

10 **Example 7a (8S)**

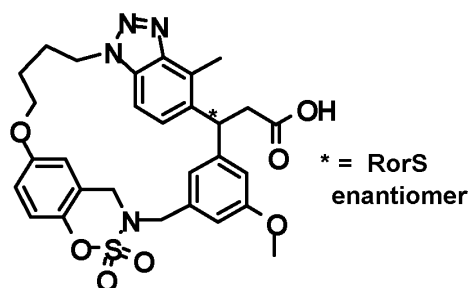
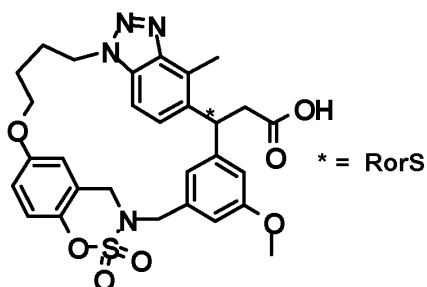
HRMS calculated for C<sub>29</sub>H<sub>30</sub>N<sub>4</sub>O<sub>6</sub>S: 562.1886; [M+H]<sup>+</sup> found: 563.1962 ( $\delta$ =0.6 ppm)

**Example 7b (8R)**

HRMS calculated for C<sub>29</sub>H<sub>30</sub>N<sub>4</sub>O<sub>6</sub>S: 562.1886; [M+H]<sup>+</sup> found: 563.1962 ( $\delta$ =0.6 ppm)

- 15 **<sup>1</sup>H-NMR** (400 MHz, DMSO-d<sub>6</sub>)  $\delta$  ppm: 12.12 (m, 1 H), 7.69 (d, 1 H), 7.49 (dd, 1 H), 7.41 (d, 1 H), 7.3 (d, 1 H), 7 (d, 1 H), 6.8 (dd, 1 H), 6.55 (d, 1 H), 5.85 (d, 1 H), 4.75 (m, 3 H), 4.11-3.92 (d, 2 H), 4-3.85 (d, 2 H), 3.62/3.4 (m, 2 H), 3.05/2.95 (dd, 2 H), 2.65/2.31 (s, 6 H), 2.2/2.08 (m, 2 H), 1.8/1.65 (m, 2 H)

- 20 **EXAMPLE 8 :** [5-Methoxy-31-methyl-27,27-dioxo-21,26-dioxa-27 $\lambda^6$ -thia-1,14,15,16-tetraazahexacyclo[20.5.3.1<sup>3,7</sup>.1<sup>9,13</sup>.0<sup>12,16</sup>.0<sup>25,29</sup>]dotriaconta-3(32),4,6,9(31),10,12,14,22,24,29-decaen-8-yl]acetic acid



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**STEP 1 : Preparation of ethyl 3-[3-(hydroxymethyl)-5-methoxyphenyl]-3-(1-{4-[(4-methoxyphenyl)methoxy]butyl}-4-methyl-1*H*-benzotriazol-5-yl)propanoate**

5 Using General Procedure 6 starting from ethyl (2*E*)-3-(1-{4-[(4-methoxyphenyl)methoxy]butyl}-4-methyl-1*H*-benzotriazol-5-yl)prop-2-enoate (1 eq.) and [3-methoxy-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]methanol (1 eq.) as reactants, the title compound (yellow oil, 30% yield) was obtained.

<sup>1</sup>H-NMR (400 MHz, DMSO-d<sub>6</sub>) δ ppm: 7.59 (d, 1 H), 7.5 (d, 1 H), 7.2 (d, 2 H), 6.88 (d, 2 H),  
10 6.3-6.15 (3sl, 3 H), 5.1 (t, 1 H), 4.81 (t, 1 H), 4.62 (t, 2 H), 4.4 (d, 2 H), 4.3 (s, 2 H), 3.95 (q, 2 H), 3.71 (s, 6 H), 3.39 (t, 2 H), 3.12 (m, 2 H), 2.75 (s, 3 H), 1.92 (m, 2 H), 1.5 (m, 2 H), 1 (t, 3 H)

**STEP 2 : Preparation of ethyl 3-(3-{[6-(benzyloxy)-2,2-dioxo-2*H*-1,2λ<sup>6</sup>,3-benzoxathiazin-3(4*H*)-yl]methyl}-5-methoxyphenyl)-3-(1-{4-[(4-methoxyphenyl)methoxy]butyl}-4-methyl-1*H*-benzotriazol-5-yl)propanoate**

Using General Procedure 7 starting from ethyl 3-[3-(hydroxymethyl)-5-methoxyphenyl]-3-(1-{4-[(4-methoxyphenyl)methoxy]butyl}-4-methyl-1*H*-benzotriazol-5-yl)propanoate (1 eq.) and  
20 6-(benzyloxy)-3,4-dihydro-2*H*-1,2λ<sup>6</sup>,3-benzoxathiazine-2,2-dione (1.1 eq.) as reactants, the title compound (88% yield) was obtained.

<sup>1</sup>H-NMR (400 MHz, DMSO-d<sub>6</sub>) δ ppm: 7.72-7.3 (m, 5 H), 7.58 (d, 1 H), 7.48 (d, 1 H), 7.2 (d, 2 H), 7-6.9 (m, 3 H), 6.91/6.8/6.72 (3d, 3 H), 6.87 (d, 2 H), 5.05 (s, 2 H), 4.81 (t, 1 H), 4.62 (t, 2 H), 4.55 (s, 2 H), 4.3/4.23 (2s, 4 H), 3.91 (q, 2 H), 3.7 (2s, 6 H), 3.35 (t, 2 H), 3.12 (d, 2 H),  
25 2.78 (s, 3 H), 1.9 (m, 2 H), 1.48 (m, 2 H), 1 (t, 3 H)

**STEP 3 : Preparation of ethyl 3-[1-(4-hydroxybutyl)-4-methyl-1*H*-benzotriazol-5-yl]-3-{3-[(6-hydroxy-2,2-dioxo-2*H*-1,2λ<sup>6</sup>,3-benzoxathiazin-3(4*H*)-yl)methyl]-5-methoxyphenyl}propanoate**

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Using General Procedure 8 starting from ethyl 3-(3-{{6-(benzyloxy)-2,2-dioxo-2*H*-1,2λ<sup>6</sup>,3-benzoxathiazin-3(4*H*)-yl)methyl}-5-methoxyphenyl)-3-(1-{4-[(4-methoxyphenyl)methoxy]butyl}-4-methyl-1*H*-benzotriazol-5-yl)propanoate (1 eq.) as a reactant, the title compound (white solid, 96% yield) was obtained.

- 5 <sup>1</sup>H-NMR (400 MHz, DMSO-d<sub>6</sub>) δ ppm: 9.6/4.4 (s+t, 2 H), 7.6 (d, 1 H), 7.5 (d, 1 H), 6.91 (d, 1 H), 6.9 (d, 1 H), 6.8/6.72/6.6 (3sl, 3 H), 6.71 (dd, 1 H), 4.81 (t, 1 H), 4.62 (t, 2 H), 4.52 (s, 2 H), 4.21 (s, 2 H), 3.92 (q, 2 H), 3.7 (s, 3 H), 3.4 (q, 2 H), 3.17 (d, 2 H), 2.78 (s, 3 H), 1.9 (m, 2 H), 1.38 (m, 2 H), 1 (t, 3 H)

10 **STEP 4 : Preparation of ethyl 3-[1-(4-bromobutyl)-4-methyl-1*H*-benzotriazol-5-yl]-3-{{3-[(6-hydroxy-2,2-dioxo-2*H*-1,2λ<sup>6</sup>,3-benzoxathiazin-3(4*H*)-yl)methyl]-5-methoxyphenyl}propanoate**

Using General Procedure 9 starting from ethyl 3-[1-(4-hydroxybutyl)-4-methyl-1*H*-

- 15 benzotriazol-5-yl]-3-{{3-[(6-hydroxy-2,2-dioxo-2*H*-1,2λ<sup>6</sup>,3-benzoxathiazin-3(4*H*)-yl)methyl]-5-methoxyphenyl}propanoate (1 eq.) as a reactant, the title compound (white solid, 82% yield) was obtained.

- <sup>1</sup>H-NMR (400 MHz, DMSO-d<sub>6</sub>) δ ppm: 9.61 (m, 1 H), 7.64 (d, 1 H), 7.51 (d, 1 H), 6.91/6.81 (2sl, 2 H), 6.88 (d, 1 H), 6.73 (sl, 1 H), 6.71 (dd, 1 H), 6.58 (d, 1 H), 4.82 (t, 1 H), 4.69 (t, 2 H),  
20 4.51/4.21 (2s, 4 H), 3.93 (q, 2 H), 3.69 (s, 3 H), 3.54 (t, 2 H), 3.15 (d, 2 H), 2.76 (s, 3 H), 1.99 (m, 2 H), 1.78 (m, 2 H), 1 (t, 3 H)

- STEP 5 : Preparation of ethyl [5-methoxy-31-methyl-27,27-dioxo-21,26-dioxa-27λ<sup>6</sup>-thia-1,14,15,16-tetraazahexacyclo[20.5.3.1<sup>3,7</sup>.1<sup>9,13</sup>.0<sup>12,16</sup>.0<sup>25,29</sup>]dotriaconta-3(32),4,6,9(31),10,12,14,22,24,29-decaen-8-yl]acetate**
- 25

Using General Procedure 11 starting from ethyl 3-[1-(4-bromobutyl)-4-methyl-1*H*-benzotriazol-5-yl]-3-{{3-[(6-hydroxy-2,2-dioxo-2*H*-1,2λ<sup>6</sup>,3-benzoxathiazin-3(4*H*)-yl)methyl]-5-methoxyphenyl}propanoate (1 eq.) as a reactant, the title compound (95% yield) was  
30 obtained.

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<sup>1</sup>H-NMR (400 MHz, DMSO-d<sub>6</sub>) δ ppm: 7.6 (d, 1 H), 7.33 (d, 1 H), 7.09/6.78/6.37 (3sl, 3 H), 6.93 (d, 1 H), 6.71 (dd, 1 H), 5.98 (d, 1 H), 4.85-4.67 (m, 3 H), 4.12-3.9 (2dd, 4 H), 3.94 (m, 2 H), 3.81 (s, 3 H), 3.52/3.42 (2m, 2 H), 3.2/3.08 (2dd, 2 H), 2.72 (s, 3 H), 2.19/1.98 (2m, 2 H), 1.68/1.48 (2m, 2 H), 1.02 (t, 3 H)

5

#### STEP 6 : Preparation of EXAMPLE 8

Using General Procedure 12 starting from ethyl [5-methoxy-31-methyl-27,27-dioxo-21,26-dioxa-27λ<sup>6</sup>-thia-1,14,15,16-tetraazahexacyclo[20.5.3.1<sup>3,7</sup>.1<sup>9,13</sup>.0<sup>12,16</sup>.0<sup>25,29</sup>]dotriaconta-

10 3(32),4,6,9(31),10,12,14,22,24,29-decaen-8-yl]acetate (1 eq.) as a reactant, the title compound (white solid, 28% yield) was obtained.

The enantiopure products were obtained by chromatographic separation on chiral column.

#### Example 8a (E1)

15 HRMS calculated for C<sub>29</sub>H<sub>30</sub>N<sub>4</sub>O<sub>7</sub>S: 578.1835; [M+H]<sup>+</sup> found: 579.1911 (δ=0.5 ppm)

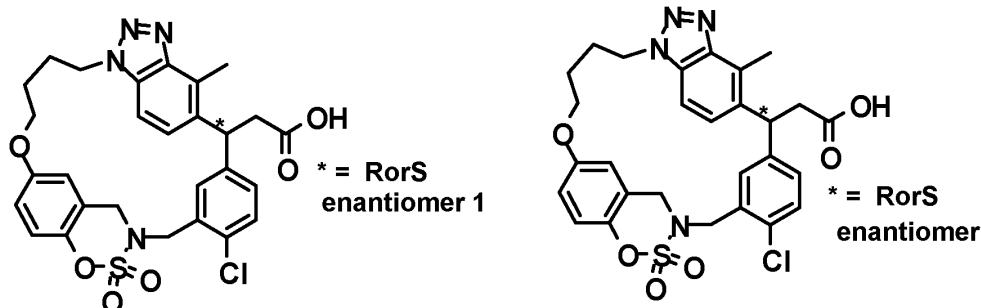
#### Example 8b (E2)

HRMS calculated for C<sub>29</sub>H<sub>30</sub>N<sub>4</sub>O<sub>7</sub>S: 578.1835; [M+H]<sup>+</sup> found: 579.1912 (δ=0.7 ppm)

20 <sup>1</sup>H-NMR (400 MHz, DMSO-d<sub>6</sub>) δ ppm: 12.15 (m, 1 H), 7.6 (d, 1 H), 7.31 (d, 1 H), 7.31 (2dd, 4 H), 7.1/6.8/6.38 (3sl, 3 H), 6.95 (d, 1 H), 6.71 (dd, 1 H), 5.98 (d, 1 H), 4.85-4.67 (m, 3 H), 3.81 (s, 3 H), 3.68/3.41 (2m, 2 H), 3.1/2.98 (2dd, 2 H), 2.71 (s, 3 H), 2.19/1.98 (2m, 2 H), 1.68/1.48 (2m, 2 H)

25 **EXAMPLE 9 :** [4-Chloro-31-methyl-27,27-dioxo-21,26-dioxa-27λ<sup>6</sup>-thia-1,14,15,16-tetraazahexacyclo[20.5.3.1<sup>3,7</sup>.1<sup>9,13</sup>.0<sup>12,16</sup>.0<sup>25,29</sup>]dotriaconta-3(32),4,6,9(31),10,12,14,22,24,29-decaen-8-yl]acetic acid

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**STEP 1 : Preparation of ethyl 3-[4-chloro-3-(hydroxymethyl)phenyl]-3-(1-{4-[(4-methoxyphenyl)methoxy]butyl}-4-methyl-1*H*-benzotriazol-5-yl)propanoate**

5

Using General Procedure 6 starting from ethyl (2*E*)-3-(1-{4-[(4-methoxyphenyl)methoxy]butyl}-4-methyl-1*H*-benzotriazol-5-yl)prop-2-enoate (1 eq.) and [2-chloro-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]methanol (2 eq.) as reactants, the title compound (yellow oil, 83% yield) was obtained.

10 **<sup>1</sup>H-NMR** (400 MHz, DMSO-*d*<sub>6</sub>) δ ppm: 7.6 (d, 1 H), 7.48 (d, 1 H), 7.47 (d, 1 H), 7.3 (d, 1 H), 7.22 (dd, 1 H), 7.19 (d, 2 H), 6.88 (d, 2 H), 5.3 (t, 1 H), 4.89 (t, 1 H), 4.63 (t, 2 H), 4.49 (d, 2 H), 4.3 (s, 2 H), 3.92 (q, 2 H), 3.71 (s, 3 H), 3.39 (t, 2 H), 3.17 (m, 2 H), 2.75 (s, 3 H), 1.91 (m, 2 H), 1.49 (m, 2 H), 1 (t, 3 H)

15 **STEP 2 : Preparation of ethyl 3-(3-{[6-(benzyloxy)-2,2-dioxo-2*H*-1,2λ<sup>6</sup>,3-benzoxathiazin-3(4*H*)-yl]methyl}-4-chlorophenyl)-3-(1-{4-[(4-methoxyphenyl)methoxy]butyl}-4-methyl-1*H*-benzotriazol-5-yl)propanoate**

Using General Procedure 7 starting from ethyl 3-[4-chloro-3-(hydroxymethyl)phenyl]-3-(1-{4-[(4-methoxyphenyl)methoxy]butyl}-4-methyl-1*H*-benzotriazol-5-yl)propanoate (1 eq.) and 6-(benzyloxy)-3,4-dihydro-2*H*-1,2λ<sup>6</sup>,3-benzoxathiazine-2,2-dione (1.5 eq.) as reactants, the title compound (92% yield) was obtained.

20 **<sup>1</sup>H-NMR** (400 MHz, DMSO-*d*<sub>6</sub>) δ ppm: 7.6 (d, 1 H), 7.5-7.3 (m, 8 H), 7.49 (d, 1 H), 7.18 (d, 2 H), 7.09 (d, 1 H), 7.04 (dd, 1 H), 6.96 (d, 1 H), 6.86 (d, 2 H), 5.09 (s, 2 H), 4.89 (t, 1 H),

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4.63 (t, 2 H), 4.56/4.34 (2s, 4 H), 4.3 (s, 2 H), 3.94 (q, 2 H), 3.72 (s, 3 H), 3.36 (t, 2 H), 3.2 (2ddd, 2 H), 2.77 (s, 3 H), 1.9 (m, 2 H), 1.46 (m, 2 H), 1 (t, 3 H)

**STEP 3 : Preparation of ethyl 3-{4-chloro-3-[(6-hydroxy-2,2-dioxo-2*H*-1,2λ<sup>6</sup>,3-benzoxathiazin-3(4*H*)-yl)methyl]phenyl}-3-[1-(4-hydroxybutyl)-4-methyl-1*H*-benzotriazol-5-yl]propanoate**

Using General Procedure 8 starting from ethyl 3-(3-{[6-(benzyloxy)-2,2-dioxo-2*H*-1,2λ<sup>6</sup>,3-benzoxathiazin-3(4*H*)-yl)methyl]-4-chlorophenyl}-3-(1-{4-[(4-methoxyphenyl)methoxy]butyl}-4-methyl-1*H*-benzotriazol-5-yl)propanoate (1 eq.) as a reactant, the title compound (77% yield) was obtained.

**<sup>1</sup>H-NMR** (400 MHz, DMSO-d<sub>6</sub>) δ ppm: 9.68 (m, 1 H), 7.64 (d, 1 H), 7.51 (d, 1 H), 7.49 (d, 1 H), 7.39 (dd, 1 H), 7.31 (d, 1 H), 6.95 (d, 1 H), 6.77 (dd, 1 H), 6.63 (d, 1 H), 4.89 (t, 1 H), 4.66 (t, 2 H), 4.51/4.33 (2s, 4 H), 4.41 (t, 2 H), 3.95 (q, 2 H), 3.38 (q, 2 H), 3.23/3.17 (2dd, 2 H), 2.76 (s, 3 H), 1.91 (m, 2 H), 1.37 (m, 2 H), 1.01 (t, 3 H)

**STEP 4 : Preparation of ethyl 3-[1-(4-bromobutyl)-4-methyl-1*H*-benzotriazol-5-yl]-3-{4-chloro-3-[(6-hydroxy-2,2-dioxo-2*H*-1,2λ<sup>6</sup>,3-benzoxathiazin-3(4*H*)-yl)methyl]phenyl}propanoate**

Using General Procedure 9 starting from ethyl 3-{4-chloro-3-[(6-hydroxy-2,2-dioxo-2*H*-1,2λ<sup>6</sup>,3-benzoxathiazin-3(4*H*)-yl)methyl]phenyl}-3-[1-(4-hydroxybutyl)-4-methyl-1*H*-benzotriazol-5-yl]propanoate (1 eq.) as a reactant, the title compound (79% yield) was obtained.

**<sup>1</sup>H-NMR** (400 MHz, DMSO-d<sub>6</sub>) δ ppm: 9.67 (s), 7.66 (d, 1 H), 7.53 (d, 1 H), 7.49 (d, 1 H), 7.39 (d, 1 H), 7.32 (dd, 1 H), 6.95 (d, 1 H), 6.77 (dd, 1 H), 6.62 (d, 1 H), 4.89 (t, 1 H), 4.7 (t, 2 H), 4.52 (s, 2 H), 4.33 (s, 2 H), 3.95 (q, d H), 3.55 (t, 2 H), 3.2 (m, 2 H), 2.77 (s, 3 H), 2 (m, 2 H), 1.78 (m, 2 H), 1.01 (t, 3 H)

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**STEP 5 : Preparation of ethyl [4-chloro-31-methyl-27,27-dioxo-21,26-dioxa-27 $\lambda^6$ -thia-1,14,15,16-tetraazahexacyclo[20.5.3.1<sup>3,7</sup>.1<sup>9,13</sup>.0<sup>12,16</sup>.0<sup>25,29</sup>]dotriaconta-3(32),4,6,9(31),10,12,14,22,24,29-decaen-8-yl]acetate**

5 Using General Procedure 11 starting from ethyl 3-[1-(4-bromobutyl)-4-methyl-1*H*-benzotriazol-5-yl]-3-{4-chloro-3-[(6-hydroxy-2,2-dioxo-2*H*-1,2 $\lambda^6$ ,3-benzoxathiazin-3(4*H*)-yl)methyl]phenyl} propanoate (1 eq.) as a reactant, the title compound (97% yield) was obtained.

10 <sup>1</sup>H-NMR (400 MHz, DMSO-d<sub>6</sub>)  $\delta$  ppm: 7.69 (d, 1 H), 7.64 (dd, 1 H), 7.57 (d, 1 H), 7.45 (d, 1 H), 6.99 (d, 1 H), 6.8 (dd, 1 H), 6.8 (d, 1 H), 5.86 (d, 1 H), 4.82 (m, 2 H), 4.79 (m, 1 H), 4.24/4.05 (dd, 2 H), 4.01/3.84 (dd, 2 H), 3.93 (q, 2 H), 3.67/3.47 (2m, 2 H), 3.21/3.08 (2dd, 2 H), 2.63 (s, 3 H), 2.2/2.05 (2m, 2 H), 1.8/1.64 (2m, 2 H), 1 (t, 3 H)

**STEP 6 : Preparation of EXAMPLE 9**

15

Using General Procedure 12 starting from ethyl [4-chloro-31-methyl-27,27-dioxo-21,26-dioxa-27 $\lambda^6$ -thia-1,14,15,16-tetraazahexacyclo[20.5.3.1<sup>3,7</sup>.1<sup>9,13</sup>.0<sup>12,16</sup>.0<sup>25,29</sup>]dotriaconta-3(32),4,6,9(31),10,12,14,22,24,29-decaen-8-yl]acetate (1 eq.) as a reactant, the title compound (white solid, 56% yield) was obtained.

20 The enantiopure products were obtained by chromatographic separation on chiral column.

**Example 9a (E1)**

HRMS calculated for C<sub>28</sub>H<sub>27</sub>ClN<sub>4</sub>O<sub>6</sub>S: 582.1340; [M+H]<sup>+</sup> found: 583.1418 ( $\delta$ =0.9 ppm)

25 **Example 9b (E2)**

HRMS calculated for C<sub>28</sub>H<sub>27</sub>ClN<sub>4</sub>O<sub>6</sub>S: 582.1340; [M+H]<sup>+</sup> found: 583.1417 ( $\delta$ =0.8 ppm)

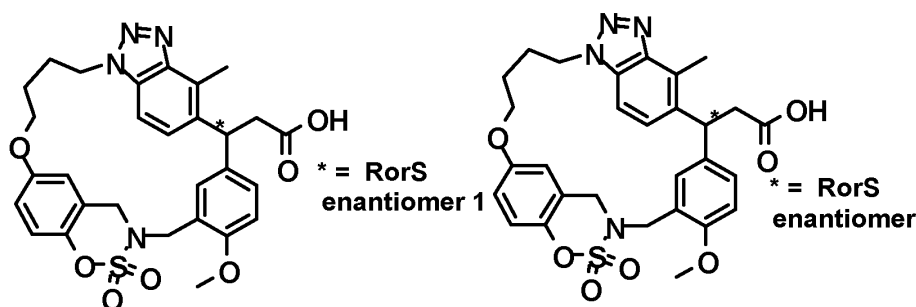
<sup>1</sup>H-NMR (400 MHz, DMSO-d<sub>6</sub>)  $\delta$  ppm: 12.28 (m, 1 H), 7.69 (d, 1 H), 7.64 (dd, 1 H), 7.57 (d, 1 H), 7.44 (d, 1 H), 6.99 (d, 1 H), 6.79 (dd, 1 H), 6.78 (d, 1 H), 5.85 (d, 1 H), 4.84-4.7 (m, 1 H), 4.8 (t, 2 H), 4.23/4.05 (dd, 2 H), 4/3.83 (dd, 2 H), 3.67/3.45 (2m, 2 H), 3.09/2.96 (2dd, 2 H), 2.63 (s, 3 H), 2.2/2.08 (2m, 2 H), 1.82/1.63 (2m, 2 H)

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**EXAMPLE 10 :** [4-Methoxy-31-methyl-27,27-dioxo-21,26-dioxa-27 $\lambda^6$ -thia-1,14,15,16-tetraazahehexacyclo[20.5.3.1<sup>3,7</sup>.1<sup>9,13</sup>.0<sup>12,16</sup>.0<sup>25,29</sup>]dotriaconta-3(32),4,6,9(31),10,12,14,22,24,29-decaen-8-yl]acetic acid

5



**STEP 1 :** Preparation of ethyl 3-[3-(hydroxymethyl)-4-methoxyphenyl]-3-(1-{4-[(4-methoxyphenyl)methoxy]butyl}-4-methyl-1*H*-benzotriazol-5-yl)propanoate

10

Using General Procedure 6 starting from ethyl (2*E*)-3-(1-{4-[(4-methoxyphenyl)methoxy]butyl}-4-methyl-1*H*-benzotriazol-5-yl)prop-2-enoate (1 eq.) and [2-methoxy-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]methanol (1.4 eq.) as reactants, the title compound (yellow oil, 68% yield) was obtained.

**<sup>1</sup>H-NMR** (400 MHz, DMSO-*d*<sub>6</sub>)  $\delta$  ppm: 7.6 (d, 1 H), 7.45 (d, 1 H), 7.28 (d, 1 H), 7.2 (d, 2 H), 7.19 (dd, 1 H), 6.9 (d, 2 H), 6.82 (d, 1 H), 4.9 (t, 1 H), 4.82 (t, 1 H), 4.65 (t, 2 H), 4.41 (d, 2 H), 4.31 (s, 2 H), 3.92 (q, 2 H), 3.71 (2s, 6 H), 3.4 (t, 2 H), 3.12 (dd, 2 H), 2.78 (s, 3 H), 1.91 (m, 2 H), 1.5 (m, 2 H), 1 (t, 3 H)

**STEP 2 :** Preparation of ethyl 3-(3-{[6-(benzyloxy)-2,2-dioxo-2*H*-1,2 $\lambda^6$ ,3-benzoxathiazin-3(4*H*)-yl]methyl}-4-methoxyphenyl)-3-(1-{4-[(4-methoxyphenyl)methoxy]butyl}-4-methyl-1*H*-benzotriazol-5-yl)propanoate

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Using General Procedure 7 starting from 3-[3-(hydroxymethyl)-4-methoxyphenyl]-3-(1-{4-[(4-methoxyphenyl)methoxy]butyl}-4-methyl-1*H*-benzotriazol-5-yl)propanoate (1 eq.) and 6-(benzyloxy)-3,4-dihydro-2*H*-1,2λ<sup>6</sup>,3-benzoxathiazine-2,2-dione (1.1eq.) as reactants, the title compound (79% yield) was obtained.

5 <sup>1</sup>H-NMR (400 MHz, DMSO-d<sub>6</sub>) δ ppm: 7.6 (d, 1 H), 7.49 (d, 1 H), 7.45-7.3 (m, 5 H), 7.28 (d, 1 H), 7.21 (dd, 1 H), 7.18 (d, 2 H), 7-6.9 (m, 3 H), 6.85 (d, 3 H), 5.08 (s, 2 H), 4.8 (t, 1 H), 4.65 (t, 2 H), 4.52 (s, 2 H), 4.31 (s, 2 H), 4.2 (s, 2 H), 3.92 (q, 2 H), 3.72/3.65 (2s, 6 H), 3.38 (t, 2 H), 3.12 (d, 2 H), 2.79 (s, 3 H), 1.9 (m, 2 H), 1.45 (m, 2 H), 1 (t, 3 H)

10 **STEP 3 : Preparation of ethyl 3-[1-(4-hydroxybutyl)-4-methyl-1*H*-benzotriazol-5-yl]-3-{3-[(6-hydroxy-2,2-dioxo-2*H*-1,2λ<sup>6</sup>,3-benzoxathiazin-3(4*H*)-yl)methyl]-4-methoxyphenyl}propanoate**

Using General Procedure 8 starting from ethyl 3-(3-{[6-(benzyloxy)-2,2-dioxo-2*H*-1,2λ<sup>6</sup>,3-benzoxathiazin-3(4*H*)-yl]methyl}-4-methoxyphenyl)-3-(1-{4-[(4-methoxyphenyl)methoxy]butyl}-4-methyl-1*H*-benzotriazol-5-yl)propanoate (1 eq.) as a reactant, the title compound (white solid, 81% yield) was obtained.

15 <sup>1</sup>H-NMR (400 MHz, DMSO-d<sub>6</sub>) δ ppm: 9.6/4.41 (s+t, 2 H), 7.65 (d, 1 H), 7.5 (d, 1 H), 7.28 (d, 1 H), 7.21 (dd, 1 H), 6.9 (d, 1 H), 6.87 (d, 1 H), 6.71 (dd, 1 H), 6.6 (d, 1 H), 4.82 (t, 1 H),  
20 4.65 (t, 2 H), 4.5 (s, 2 H), 4.2 (s, 2 H), 3.95 (q, 2 H), 3.7 (s, 3 H), 3.4 (q, 2 H), 3.15 (d, 2 H), 2.75 (s, 3 H), 1.91 (m, 2 H), 1.38 (m, 2 H), 1.02 (t, 3 H)

25 **STEP 4 : Preparation of ethyl 3-[1-(4-bromobutyl)-4-methyl-1*H*-benzotriazol-5-yl]-3-{3-[(6-hydroxy-2,2-dioxo-2*H*-1,2λ<sup>6</sup>,3-benzoxathiazin-3(4*H*)-yl)methyl]-4-methoxyphenyl}propanoate**

Using General Procedure 9 starting from ethyl 3-[1-(4-hydroxybutyl)-4-methyl-1*H*-benzotriazol-5-yl]-3-{3-[(6-hydroxy-2,2-dioxo-2*H*-1,2λ<sup>6</sup>,3-benzoxathiazin-3(4*H*)-yl)methyl]-4-methoxyphenyl}propanoate (1 eq.) as a reactant, the title compound (white solid, 69% yield)  
30 was obtained.

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<sup>1</sup>H-NMR (400 MHz, DMSO-d<sub>6</sub>) δ ppm: 9.6 (s, 1 H), 7.65 (d, 1 H), 7.51 (d, 1 H), 7.25 (d, 1 H), 7.22 (dd, 1 H), 6.9 (d, 1 H), 6.82 (d, 1 H), 6.71 (dd, 1 H), 6.59 (d, 1 H), 4.85 (t, 1 H), 4.7 (t, 2 H), 4.49 (s, 2 H), 4.21 (s, 2 H), 3.92 (q, 2 H), 3.7 (s, 3 H), 3.55 (t, 2 H), 3.15 (d, 2 H), 2.75 (s, 3 H), 2 (m, 2 H), 1.8 (m, 2 H), 1 (t, 3 H)

5

**STEP 5 : Preparation of ethyl [4-methoxy-31-methyl-27,27-dioxo-21,26-dioxa-27λ<sup>6</sup>-thia-1,14,15,16-tetraazahexacyclo[20.5.3.1<sup>3,7</sup>.1<sup>9,13</sup>.0<sup>12,16</sup>.0<sup>25,29</sup>]dotriaconta-3(32),4,6,9(31),10,12,14,22,24,29-decaen-8-yl]acetate**

10 Using General Procedure 11 starting from ethyl 3-[1-(4-bromobutyl)-4-methyl-1*H*-benzotriazol-5-yl]-3-{3-[(6-hydroxy-2,2-dioxo-2*H*-1,2λ<sup>6</sup>,3-benzoxathiazin-3(4*H*)-yl)methyl]-4-methoxyphenyl}propanoate (1 eq.) as a reactant, the title compound (70% yield) was obtained.

15 <sup>1</sup>H-NMR (400 MHz, DMSO-d<sub>6</sub>) δ ppm: 7.69 (d, 1 H), 7.55 (dd, 1 H), 7.45 (d, 1 H), 7.09 (d, 1 H), 6.95 (d, 1 H), 6.78 (dd, 1 H), 6.59 (d, 1 H), 5.8 (d, 1 H), 4.78 (m, 3 H), 4.12/3.92 (2d, 2 H), 4.02/3.8 (2d, 2 H), 3.92 (q, 2 H), 3.81 (s, 3 H), 3.61/3.4 (2m, 2 H), 3.12/3.02 (2dd, 2 H), 2.62 (s, 3 H), 2.2/2.1 (2m, 2 H), 1.8/1.62 (2m, 2 H), 1.02 (t, 3 H)

**STEP 6 : Preparation of EXAMPLE 10**

20

Using General Procedure 12 starting from ethyl [4-methoxy-31-methyl-27,27-dioxo-21,26-dioxa-27λ<sup>6</sup>-thia-1,14,15,16-tetraazahexacyclo[20.5.3.1<sup>3,7</sup>.1<sup>9,13</sup>.0<sup>12,16</sup>.0<sup>25,29</sup>]dotriaconta-3(32),4,6,9(31),10,12,14,22,24,29-decaen-8-yl]acetate (1 eq.) as a reactant, the title compound (white solid, 88% yield) was obtained.

25 The enantiopure products were obtained by chromatographic separation on chiral column.

**Example 10a (E1)**

HRMS calculated for C<sub>29</sub>H<sub>30</sub>N<sub>4</sub>O<sub>7</sub>S: 578.1835; [M+H]<sup>+</sup> found: 579.1911 (δ=0.5 ppm)

30 **Example 10b (E2)**

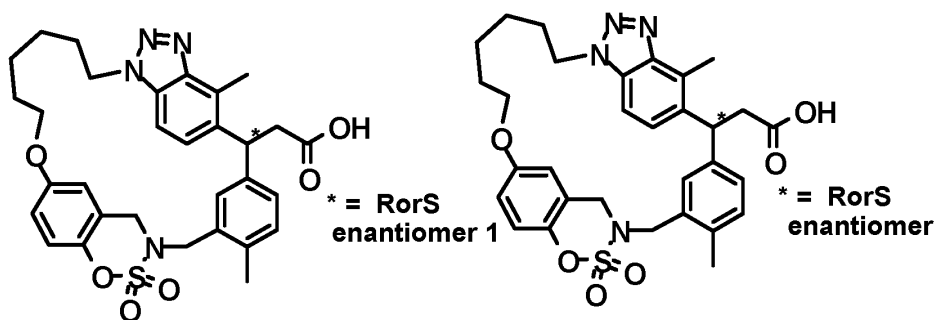
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**HRMS** calculated for  $C_{29}H_{30}N_4O_7S$ : 578.1835;  $[M+H]^+$  found: 579.1911 ( $\delta=0.5$  ppm)

**$^1H$ -NMR** (400 MHz, DMSO- $d_6$ )  $\delta$  ppm: 12.15 (m, 1 H), 7.69 (d, 1 H), 7.55 (dd, 1 H), 7.41 (d, 1 H), 7.09 (d, 1 H), 6.95 (d, 1 H), 6.78 (dd, 1 H), 6.55 (d, 1 H), 5.79 (d, 1 H), 4.75 (m, 3 H), 4.12/3.92 (2d, 2 H), 4.02/3.8 (2d, 2 H), 3.8 (s, 3 H), 3.61/3.4 (2m, 2 H), 3.12/2.95 (2dd, 2 H),  
 5 2.62 (s, 3 H), 2.2/2.1 (2m, 2 H), 1.8/1.62 (2m, 2 H)

**EXAMPLE 11** : [4,33-Dimethyl-29,29-dioxo-23,28-dioxa-29 $\lambda^6$ -thia-1,14,15,16-tetraazahexacyclo[22.5.3.1<sup>3,7</sup>.1<sup>9,13</sup>.0<sup>12,16</sup>.0<sup>27,31</sup>]tetratriaconta-3(34),4,6,9(33),10,12,14,24,26,31-decaen-8-yl]acetic acid

10



#### STEP A1 : Preparation of *N*-[6-(benzyloxy)hexyl]-3-methyl-2-nitroaniline

15 Using General Procedure 2 STEP 1 starting from 1-fluoro-3-methyl-2-nitrobenzene (1 eq.) and 6-benzyloxyhexan-1-amine (1.2 eq.) as reactants, the title compound (53% yield) was obtained.

**$^1H$ -NMR** (400 MHz, DMSO- $d_6$ )  $\delta$  ppm: 7.35-7.2 (m, 6 H), 6.78 (d, 1 H), 6.52 (d, 1 H), 6.39 (t, 1 H), 4.42 (s, 2 H), 3.41 (t, 2 H), 3.15 (q, 2 H), 2.29 (s, 3 H), 1.55 (m, 4 H), 1.32 (m, 4 H)

#### 20 STEP A2: Preparation of *N*-[6-(benzyloxy)hexyl]-4-bromo-3-methyl-2-nitroaniline

Using General Procedure 2 STEP 2 starting from *N*-[6-(benzyloxy)hexyl]-3-methyl-2-nitroaniline (1 eq.) as a reactant, the title compound (99% yield) was obtained.

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<sup>1</sup>H-NMR (400 MHz, DMSO-d<sub>6</sub>) δ ppm: 7.5 (d, 1 H), 7.3 (m, 5 H), 6.7 (d, 1 H), 6.12 (t), 4.43 (s, 2 H), 3.4 (t, 2 H), 3.1 (q, 2 H), 2.25 (s, 3 H), 1.53/1.34 (2m, 8 H)

**STEP A3 : Preparation of *N*<sup>1</sup>-[6-(benzyloxy)hexyl]-4-bromo-3-methylbenzene-1,2-diamine**

Using General Procedure 2 STEP 3 starting from *N*-[6-(benzyloxy)hexyl]-4-bromo-3-methyl-2-nitroaniline (1 eq., 25.3 mmol) as a reactant, the title compound (67% yield) was obtained.

<sup>1</sup>H-NMR (400 MHz, DMSO-d<sub>6</sub>) δ ppm: 7.3 (m, 5 H), 6.7 (d, 1 H), 6.23 (d, 1 H), 4.59 (sl, 2 H), 4.51 (t, 1 H), 4.44 (s, 2 H), 3.42 (t, 2 H), 2.96 (q, 2 H), 2.16 (s, 3 H), 1.56 (m, 4 H), 1.37 (m, 4 H)

**STEP A4 : Preparation of 1-[6-(benzyloxy)hexyl]-5-bromo-4-methyl-1*H*-benzotriazole**

Using General Procedure 2 STEP 4 starting from *N*<sup>1</sup>-[6-(benzyloxy)hexyl]-4-bromo-3-methylbenzene-1,2-diamine (1 eq.) as a reactant, the title compound (28% yield) was obtained.

<sup>1</sup>H-NMR (400 MHz, DMSO-d<sub>6</sub>) δ ppm: 7.68 (2d, 2 H), 7.35-7.2 (m, 5 H), 4.68 (t, 2 H), 4.4 (s, 2 H), 3.39 (t, 2 H), 2.71 (s, 3 H), 1.9 (m, 2 H), 1.5 (m, 2 H), 1.32 (m, 2 H), 1.22 (m, 2 H)

**STEP A5 : Preparation of ethyl (2*E*)-3-{1-[6-(benzyloxy)hexyl]-4-methyl-1*H*-benzotriazol-5-yl}prop-2-enoate**

Using General Procedure 2 STEP 5 starting from 1-[6-(benzyloxy)hexyl]-5-bromo-4-methyl-1*H*-benzotriazole (1 eq.) as a reactant, the title compound (22% yield) was obtained.

<sup>1</sup>H-NMR (400 MHz, DMSO-d<sub>6</sub>) δ ppm: 8 (dJ=16Hz, 1 H), 7.91 (d, 1 H), 7.7 (d, 1 H), 7.32-7.22 (m, 5 H), 6.62 (d, 1 H), 4.69 (t, 2 H), 4.4 (s, 2 H), 4.2 (q, 2 H), 3.38 (t, 2 H), 2.8 (s, 3 H), 1.9 (m, 2 H), 1.5 (m, 2 H), 1.35-1.2 (m, 4 H), 1.28 (t, 3 H)

**STEP 1 : Preparation of ethyl 3-{1-[6-(benzyloxy)hexyl]-4-methyl-1*H*-benzotriazol-5-yl}-3-[3-(hydroxymethyl)-4-methylphenyl]propanoate**

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Using General Procedure 6 starting from ethyl (2*E*)-3-{1-[6-(benzyloxy)hexyl]-4-methyl-1*H*-benzotriazol-5-yl}prop-2-enoate (1 eq.) and [2-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]methanol (1.5 eq.) as reactants, the title compound (14% yield) was obtained.

<sup>1</sup>H-NMR (400 MHz, DMSO-d<sub>6</sub>) δ ppm: 7.6 (d, 1 H), 7.45 (d, 1 H), 7.3 (s, 1 H), 7.3 (m, 5 H), 7.1 (d, 1 H), 7 (d, 1 H), 5 (t, 1 H), 4.85 (t, 1 H), 4.65 (t, 2 H), 4.4 (2s, 4 H), 3.95 (q, 2 H), 3.35 (t, 2 H), 3.15 (m, 2 H), 2.75 (s, 3 H), 2.15 (s, 3 H), 1.85 (m, 2 H), 1.5 (m, 2 H), 1.35-1.2 (m, 4 H), 1 (t, 3 H)

**STEP 2 : Preparation of ethyl 3-(3-{[6-(benzyloxy)-2,2-dioxo-2*H*-1,2λ<sup>6</sup>,3-benzoxathiazin-3(4*H*)-yl]methyl}-4-methylphenyl)-3-{1-[6-(benzyloxy)hexyl]-4-methyl-1*H*-benzotriazol-5-yl}propanoate**

Using General Procedure 7 starting from ethyl 3-{1-[6-(benzyloxy)hexyl]-4-methyl-1*H*-benzotriazol-5-yl}-3-[3-(hydroxymethyl)-4-methylphenyl]propanoate (1 eq.) and 6-(benzyloxy)-3,4-dihydro-2*H*-1,2λ<sup>6</sup>,3-benzoxathiazine-2,2-dione (1.2 eq.) as reactants, the title compound (84% yield) was obtained.

<sup>1</sup>H-NMR (400 MHz, DMSO-d<sub>6</sub>) δ ppm: 7.61-6.93 (m, 18 H), 5.1 (s, 2 H), 4.84 (t, 1 H), 4.58 (t, 2 H), 4.42/4.21 (s, 2 H), 4.42/4.21 (s, 2 H), 4.38 (s, 2 H), 3.92 (q, 2 H), 3.32 (m, 2 H), 3.16 (m, 2 H), 2.76 (s, 3 H), 2.21 (s, 3 H), 1.83 (m, 2 H), 1.45 (m, 2 H), 1.3 (m, 2 H), 1.19 (m, 2 H), 0.97 (t, 3 H)

**STEP 3 : Preparation of ethyl 3-{3-[(6-hydroxy-2,2-dioxo-2*H*-1,2λ<sup>6</sup>,3-benzoxathiazin-3(4*H*)-yl)methyl]-4-methylphenyl}-3-[1-(6-hydroxyhexyl)-4-methyl-1*H*-benzotriazol-5-yl]propanoate**

Using General Procedure 8 starting from ethyl 3-(3-{[6-(benzyloxy)-2,2-dioxo-2*H*-1,2λ<sup>6</sup>,3-benzoxathiazin-3(4*H*)-yl]methyl}-4-methylphenyl)-3-{1-[6-(benzyloxy)hexyl]-4-methyl-1*H*-benzotriazol-5-yl}propanoate (1 eq.) as a reactant, the title compound (95% yield) was obtained.

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<sup>1</sup>H-NMR (400 MHz, DMSO-d<sub>6</sub>) δ ppm: 9.68 (m, 1 H), 7.61 (d, 1 H), 7.5 (d, 1 H), 7.21 (d, 1 H), 7.19 (dd, 1 H), 7.13 (d, 1 H), 6.99 (d, 1 H), 6.79 (dd, 1 H), 6.6 (d, 1 H), 4.84 (t, 1 H), 4.63 (t, 2 H), 4.38 (s, 2 H), 4.29 (t, 1 H), 4.2 (dd, 2 H), 3.94 (q, 2 H), 3.32 (m, 2 H), 3.17 (m, 2 H), 2.75 (s, 3 H), 2.22 (s, 3 H), 1.87 (m, 2 H), 1.38-1.15 (m, 6 H), 0.99 (t, 3 H)

5

**STEP 4 : Preparation of ethyl 3-[1-(6-bromohexyl)-4-methyl-1*H*-benzotriazol-5-yl]-3-{3-[(6-hydroxy-2,2-dioxo-2*H*-1,2λ<sup>6</sup>,3-benzoxathiazin-3(4*H*)-yl)methyl]-4-methylphenyl}propanoate**

10 Using General Procedure 9 starting from ethyl 3-{3-[(6-hydroxy-2,2-dioxo-2*H*-1,2λ<sup>6</sup>,3-benzoxathiazin-3(4*H*)-yl)methyl]-4-methylphenyl}-3-[1-(6-hydroxyhexyl)-4-methyl-1*H*-benzotriazol-5-yl]propanoate (1 eq.) as a reactant, the title compound (87% yield) was obtained.  
<sup>1</sup>H-NMR (400 MHz, DMSO-d<sub>6</sub>) δ ppm: 9.68 (m, 1 H), 7.61 (d, 1 H), 7.5 (d, 1 H), 7.21 (d, 1 H), 7.2 (dd, 1 H), 7.13 (d, 1 H), 6.99 (d, 1 H), 6.78 (dd, 1 H), 6.6 (d, 1 H), 4.84 (t, 1 H), 4.63 (t, 2 H), 4.38 (s, 2 H), 4.19 (dd, 2 H), 3.94 (q, 2 H), 3.46 (t, 2 H), 3.16 (dd, 2 H), 2.75 (s, 3 H), 2.22 (s, 3 H), 1.88 (m, 2 H), 1.74 (m, 2 H), 1.39 (m, 2 H), 1.24 (m, 2 H), 1 (t, 3 H)

15

**STEP 5 : Preparation of ethyl [4,33-dimethyl-29,29-dioxo-23,28-dioxa-29λ<sup>6</sup>-thia-1,14,15,16-tetraazahexacyclo[22.5.3.1<sup>3,7</sup>.1<sup>9,13</sup>.0<sup>12,16</sup>.0<sup>27,31</sup>]tetratriaconta-3(34),4,6,9(33),10,12,14,24,26,31-decaen-8-yl]acetate**

20

Using General Procedure 11 starting from ethyl 3-[1-(6-bromohexyl)-4-methyl-1*H*-benzotriazol-5-yl]-3-{3-[(6-hydroxy-2,2-dioxo-2*H*-1,2λ<sup>6</sup>,3-benzoxathiazin-3(4*H*)-yl)methyl]-4-methylphenyl} propanoate (1 eq.) as a reactant, the title compound (88% yield) was obtained.  
<sup>1</sup>H-NMR (400 MHz, DMSO-d<sub>6</sub>) δ ppm: 7.64 (d, 1 H), 7.46 (d, 1 H), 7.4 (dd, 1 H), 7.21 (d, 1 H), 7.15 (d, 1 H), 7.07 (d, 1 H), 6.9 (dd, 1 H), 6.45 (d, 1 H), 4.81 (t, 1 H), 4.48 (t, 2 H), 4.4/4.11 (dd, 2 H), 4.23/4.03 (dd, 2 H), 3.89 (q, 2 H), 3.8 (m, 2 H), 3.07 (d, 2 H), 2.74 (s, 3 H), 2.31 (s, 3 H), 1.97 (m, 2 H), 1.7 (m, 2 H), 1.53 (m, 2 H), 1.32 (m, 2 H), 0.99 (t, 3 H)

25

**STEP 6 : Preparation of EXAMPLE 11**

30

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Using General Procedure 12 starting from ethyl [4,33-dimethyl-29,29-dioxo-23,28-dioxa-29 $\lambda^6$ -thia-1,14,15,16-tetraazahexacyclo[22.5.3.1<sup>3,7</sup>.1<sup>9,13</sup>.0<sup>12,16</sup>.0<sup>27,31</sup>]tetratriaconta-3(34),4,6,9(33),10,12,14,24,26,31-decaen-8-yl]acetate (1 eq.) as a reactant, the title compound

(white solid, 62% yield) was obtained.

#### Example 11a (E1)

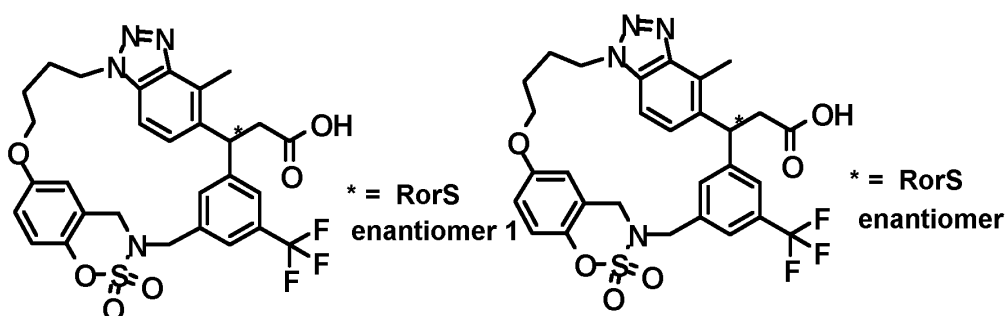
HRMS calculated for C<sub>31</sub>H<sub>34</sub>N<sub>4</sub>O<sub>6</sub>S: 590.2199; [M+H]<sup>+</sup> found: 591.2274 ( $\delta$ =0.4 ppm)

#### Example 11b (E2)

HRMS calculated for C<sub>31</sub>H<sub>34</sub>N<sub>4</sub>O<sub>6</sub>S: 590.2199; [M+H]<sup>+</sup> found: 591.2274 ( $\delta$ =0.4 ppm)

<sup>1</sup>H-NMR (400 MHz, DMSO-d<sub>6</sub>)  $\delta$  ppm: 12.13 (m, 1 H), 7.64 (d, 1 H), 7.45 (d, 1 H), 7.4 (dd, 1 H), 7.21 (d, 1 H), 7.13 (d, 1 H), 7.07 (d, 1 H), 6.9 (dd, 1 H), 6.43 (d, 1 H), 4.9 (t, 1 H), 4.66 (t, 2 H), 4.39/4.11 (dd, 2 H), 4.23/4.04 (dd, 2 H), 3.91-3.76 (m, 2 H), 2.96 (m, 2 H), 2.74 (s, 3 H), 2.31 (s, 3 H), 1.97 (m, 2 H), 1.7 (m, 2 H), 1.53 (m, 2 H), 1.32 (m, 2 H)

**EXAMPLE 12 :** [31-Methyl-27,27-dioxo-5-(trifluoromethyl)-21,26-dioxa-27 $\lambda^6$ -thia-1,14,15,16-tetraazahexacyclo[20.5.3.1<sup>3,7</sup>.1<sup>9,13</sup>.0<sup>12,16</sup>.0<sup>25,29</sup>]dotriaconta-3(32),4,6,9(31),10,12,14,22,24,29-decaen-8-yl]acetic acid



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**STEP B1: Preparation of [3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-5-(trifluoromethyl)phenyl]methanol**

Using General Procedure 3 starting from [3-bromo-5-(trifluoromethyl)phenyl]methanol (1 eq.,  
5 2.5 g, 9.8 mmol) as a reactant, the title compound (2.7 g, 91% yield) was obtained.

<sup>1</sup>H-NMR (400 MHz, DMSO-d<sub>6</sub>) δ ppm: 7.9/7.87 (m, 3 H), 5.4 (t, 1 H), 4.6 (d, 2 H), 1.3 (s, 12 H)

**STEP 1 : Preparation of ethyl 3-[3-{[6-(benzyloxy)-2,2-dioxo-2H-1,2λ<sup>6</sup>,3-benzoxathiazin-3(4H)-yl]methyl}-5-(trifluoromethyl)phenyl]-3-(1-{4-[(4-methoxyphenyl)methoxy]butyl}-4-methyl-1H-benzotriazol-5-yl)propanoate**

Using General Procedure 6 starting from ethyl (2E)-3-(1-{4-[(4-methoxyphenyl)methoxy]butyl}-4-methyl-1H-benzotriazol-5-yl)prop-2-enoate (1 eq.) and [3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-5-(trifluoromethyl)phenyl]methanol (1 eq.) as  
15 reactants, ethyl 3-[3-(hydroxymethyl)-5-(trifluoromethyl)phenyl]-3-(1-{4-[(4-methoxyphenyl)methoxy]butyl}-4-methyl-1H-benzotriazol-5-yl)propanoate (colorless oil, 16% yield) was obtained. The crude product was reacted using General Procedure 7 with 6-(benzyloxy)-3,4-dihydro-2H-1,2λ<sup>6</sup>,3-benzoxathiazine-2,2-dione (1.1 eq.) affording the title  
20 compound (85% yield).

<sup>1</sup>H-NMR (400 MHz, DMSO-d<sub>6</sub>) δ ppm: 7.68 (s, 1 H), 7.61 (d, 1 H), 7.6 (s, 1 H), 7.52 (s, 1 H), 7.5 (d, 1 H), 7.42-7.3 (m, 5 H), 7.19 (d, 2 H), 7-6.9 (m, 3 H), 6.88 (d, 2 H), 5.05 (s, 2 H), 4.95 (t, 1 H), 4.7 (t, 2 H), 4.62 (s, 2 H), 4.42/4.3 (2s, 4 H), 3.92 (q, 2 H), 3.71 (s, 3 H), 3.38 (t, 2 H), 3.21 (d, 2 H), 2.79 (s, 3 H), 1.9 (m, 2 H), 1.48 (m, 2 H), 1 (t, 3 H)

25

**STEP 2 : Preparation of ethyl 3-[1-(4-hydroxybutyl)-4-methyl-1H-benzotriazol-5-yl]-3-{3-[(6-hydroxy-2,2-dioxo-2H-1,2λ<sup>6</sup>,3-benzoxathiazin-3(4H)-yl)methyl]-5-(trifluoromethyl)phenyl}propanoate**



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Using General Procedure 8 starting from ethyl 3-[3-{[6-(benzyloxy)-2,2-dioxo-2*H*-1,2λ<sup>6</sup>,3-benzoxathiazin-3(4*H*)-yl]methyl}-5-(trifluoromethyl)phenyl]-3-(1-{4-[(4-methoxyphenyl)methoxy]butyl}-4-methyl-1*H*-benzotriazol-5-yl)propanoate (1 eq.) as a reactant, the title compound (white solid, 89% yield) was obtained.

- 5 <sup>1</sup>H-NMR (400 MHz, DMSO-d<sub>6</sub>) δ ppm: 9.59 (s), 7.67 (sl, 1 H), 7.65 (d, 1 H), 7.61 (sl, 1 H), 7.53 (sl, 1 H), 7.52 (d, 1 H), 6.8 (d, 1 H), 6.68 (dd, 1 H), 6.58 (d, 1 H), 4.95 (t, 1 H), 4.65 (t, 2 H), 4.63 (s, 2 H), 4.41 (t), 4.4 (s, 2 H), 3.95 (q, 2 H), 3.38 (q, 2 H), 3.23 (d, 2 H), 2.78 (s, 3 H), 1.91 (m, 2 H), 1.37 (m, 2 H), 1.01 (t, 3 H)

10 **STEP 3 : Preparation of ethyl 3-[1-(4-bromobutyl)-4-methyl-1*H*-benzotriazol-5-yl]-3-{3-[(6-hydroxy-2,2-dioxo-2*H*-1,2λ<sup>6</sup>,3-benzoxathiazin-3(4*H*)-yl)methyl]-5-(trifluoromethyl)phenyl}propanoate**

- Using General Procedure 9 starting from ethyl 3-[1-(4-hydroxybutyl)-4-methyl-1*H*-benzotriazol-5-yl]-3-{3-[(6-hydroxy-2,2-dioxo-2*H*-1,2λ<sup>6</sup>,3-benzoxathiazin-3(4*H*)-yl)methyl]-5-(trifluoromethyl)phenyl}propanoate (1 eq.) as a reactant, the title compound (white solid, 50% yield) was obtained.

- <sup>1</sup>H-NMR (400 MHz, DMSO-d<sub>6</sub>) δ ppm: 9.6 (s, 1 H), 7.69/7.6/7.52 (3sl, 3 H), 7.69 (d, 1 H), 7.55 (d, 1 H), 6.8 (d, 1 H), 6.7 (dd, 1 H), 6.58 (d, 1 H), 4.98 (t, 1 H), 4.7 (t, 2 H), 4.6 (s, 2 H), 4.4 (s, 2 H), 3.92 (q, 2 H), 3.55 (t, 2 H), 3.22 (d, 2 H), 2.79 (s, 3 H), 2 (m, 2 H), 1.78 (m, 2 H), 1.02 (t, 3 H)

25 **STEP 4 : Preparation of ethyl [31-methyl-27,27-dioxo-5-(trifluoromethyl)-21,26-dioxo-27λ<sup>6</sup>-thia-1,14,15,16-tetraazahexacyclo[20.5.3.1<sup>3,7</sup>.1<sup>9,13</sup>.0<sup>12,16</sup>.0<sup>25,29</sup>]dotriacont-3(32),4,6,9(31),10,12,14,22,24,29-decaen-8-yl]acetate**

- Using General Procedure 11 starting from ethyl 3-[1-(4-bromobutyl)-4-methyl-1*H*-benzotriazol-5-yl]-3-{3-[(6-hydroxy-2,2-dioxo-2*H*-1,2λ<sup>6</sup>,3-benzoxathiazin-3(4*H*)-yl)methyl]-5-(trifluoromethyl)phenyl}propanoate (1 eq.) as a reactant, the title compound (93% yield) was obtained.

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<sup>1</sup>H-NMR (400 MHz, DMSO-d<sub>6</sub>) δ ppm: 7.81/7.6/7.25 (3s, 3 H), 7.71/4.81 (2m, 2 H), 7.6 (d, 1 H), 7.35 (d, 1 H), 6.9 (d, 1 H), 6.69 (dd, 1 H), 6.02 (d, 1 H), 4.81 (t, 1 H), 4.28 (s, 2 H), 4.05 (m, 2 H), 3.95 (m, 2 H), 3.88/3.68 (2m, 2 H), 3.32/3.18 (2dd, 2 H), 2.78 (s, 3 H), 2.2/1.98 (2m, 2 H), 1.68/1.45 (2m, 2 H), 1 (t, 3 H)

5

#### STEP 5 : Preparation of EXAMPLE 12

Using General Procedure 12 starting from ethyl [31-methyl-27,27-dioxo-5-(trifluoromethyl)-21,26-dioxa-27λ<sup>6</sup>-thia-1,14,15,16-tetraazahexacyclo[20.5.3.1<sup>3,7</sup>.1<sup>9,13</sup>.0<sup>12,16</sup>.0<sup>25,29</sup>]dotriaconta-

10 3(32),4,6,9(31),10,12,14,22,24,29-decaen-8-yl]acetate (1 eq.) as a reactant, the title compound (white solid, quant.) was obtained.

The enantiopure products were obtained by chromatographic separation on chiral column.

#### Example 12a (E1)

15 HRMS calculated for C<sub>29</sub>H<sub>27</sub>F<sub>3</sub>N<sub>4</sub>O<sub>6</sub>S: 616.1603; [M+H]<sup>+</sup> found: 617.1677 (δ=0.1 ppm)

#### Example 12b (E2)

HRMS calculated for C<sub>29</sub>H<sub>27</sub>F<sub>3</sub>N<sub>4</sub>O<sub>6</sub>S: 616.1603; [M+H]<sup>+</sup> found: 617.1678 (δ=0.3 ppm)

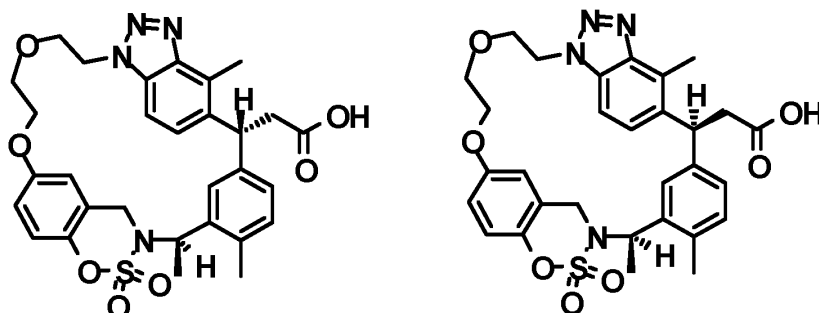
<sup>1</sup>H-NMR (400 MHz, DMSO-d<sub>6</sub>) δ ppm: 12.3 (m, 1 H), 7.84/7.58/7.23 (3s, 3 H), 7.6 (d, 1 H),  
 20 7.33 (d, 1 H), 6.89 (d, 1 H), 6.68 (dd, 1 H), 6.02 (d, 1 H), 4.89 (t, 1 H), 4.81/4.72 (2m, 2 H),  
 4.27 (s, 2 H), 4.06 (m, 2 H), 3.68/3.34 (2m, 2 H), 3.32/3.18 (2dd, 2 H), 2.78 (s, 3 H), 2.2/1.98  
 (2m, 2 H), 1.69/1.45 (2m, 2 H)

#### EXAMPLE 13 : [(2R,8R)-2,4,32-Trimethyl-28,28-dioxo-19,22,27-trioxa-28λ<sup>6</sup>-thia-

25 1,14,15,16-tetraazahexacyclo[21.5.3.1<sup>3,7</sup>.1<sup>9,13</sup>.0<sup>12,16</sup>.0<sup>26,30</sup>]tritiaconta-  
3(33),4,6,9(32),10,12,14,23,25,30-decaen-8-yl]acetic acid and  
[(2R,8S)-2,4,32-trimethyl-28,28-dioxo-19,22,27-trioxa-28λ<sup>6</sup>-thia-  
1,14,15,16-tetraazahexacyclo[21.5.3.1<sup>3,7</sup>.1<sup>9,13</sup>.0<sup>12,16</sup>.0<sup>26,30</sup>]tritiaconta-  
3(33),4,6,9(32),10,12,14,23,25,30-decaen-8-yl]acetic acid

30

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### STEP A1 : Preparation of 2-[2-(3-methyl-2-nitroanilino)ethoxy]ethan-1-ol

5 Using General Procedure 1 STEP 1 starting from 1-fluoro-3-methyl-2-nitrobenzene (1 eq.) and 2-(2-aminoethoxy)ethan-1-ol (3 eq.) as reactants, the title compound (24% yield) was obtained.

**<sup>1</sup>H-NMR** (400 MHz, DMSO-d<sub>6</sub>) δ ppm: 7.28 (t, 1 H), 6.83 (d, 1 H), 6.58 (d, 1 H), 6.43 (t, 1 H), 4.59 (t, 1 H), 3.6 (t, 2 H), 3.5 (m, 2 H), 3.45 (m, 2 H), 3.34 (q, 2 H), 2.31 (s, 3 H)

10

### STEP A2 : Preparation of 2-[2-(4-bromo-3-methyl-2-nitroanilino)ethoxy]ethan-1-ol

Using General Procedure 1 STEP 2 starting from 2-[2-(3-methyl-2-nitroanilino)ethoxy]ethanol (1 eq.) as a reactant, the title compound (67% yield) was obtained.

15 **<sup>1</sup>H-NMR** (400 MHz, DMSO-d<sub>6</sub>) δ ppm: 7.53 (d, 1 H), 6.8 (d, 1 H), 6.1 (t), 4.56 (t), 3.56 (t, 2 H), 3.5 (q, 2 H), 3.44 (t, 2 H), 3.3 (q, 2 H), 2.28 (s, 3 H)

### STEP A3 : Preparation of 2-[2-(2-amino-4-bromo-3-methylanilino)ethoxy]ethan-1-ol

20 Using General Procedure 1 STEP 3 starting from 2-[2-(4-bromo-3-methyl-2-nitroanilino)ethoxy]ethan-1-ol (1 eq.) as a reactant, the title compound (80% yield) was obtained.

**<sup>1</sup>H-NMR** (400 MHz, DMSO-d<sub>6</sub>) δ ppm: 6.72 (d, 1 H), 6.3 (d, 1 H), 4.64–4.52 (m, 4 H), 3.6 (t, 2 H), 3.51 (m, 2 H), 3.46 (m, 2 H), 3.17 (m, 2 H), 2.16 (s, 3 H)

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**STEP A4 : Preparation of 2-[2-(5-bromo-4-methyl-1*H*-benzotriazol-1-yl)ethoxy]ethan-1-ol**

5 Using General Procedure 1 STEP 4 starting from 2-[2-(2-amino-4-bromo-3-methylanilino)ethoxy]ethan-1-ol (1 eq.) as a reactant, the title compound (yellow solid, 45% yield) was obtained.

**<sup>1</sup>H-NMR** (400 MHz, DMSO-*d*<sub>6</sub>) δ ppm: 7.69 (d, 2 H), 4.87 (t, 2 H), 4.52 (m, 1 H), 3.9 (t, 2 H), 3.4-3.36 (m, 4 H), 2.72 (s, 3 H)

10

**STEP A5 : Preparation of 1-{2-[2-(benzyloxy)ethoxy]ethyl}-5-bromo-4-methyl-1*H*-benzotriazole**

To a solution of 2-[2-(5-bromo-4-methyl-1*H*-benzotriazol-1-yl)ethoxy]ethan-1-ol (1 eq., 4.1 g, 13 mmol) in DMF (7 mL/mmol, 92 mL) NaH (1.2 eq., 630 mg, 16 mmol, 60 wt% in mineral oil) was added at 0°C. The mixture was allowed to warm to RT and stirred at this temperature for 30 min. The reaction mixture was cooled to 0°C. Benzylbromide (1.2 eq., 2.7 g, 1.9 mL, 16 mmol) was added and the stirring was continued overnight at RT. The mixture was quenched with 500 mL water, extracted with 4x1000 ml EtOAc and the organic layer was washed with 20 brine, dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated to dryness to give a black oil, which was purified by normal phase silica gel chromatography using heptane-EtOAc (20:80) as an eluent to give the title compound (3.65 g, 71% yield).

**<sup>1</sup>H-NMR** (400 MHz, DMSO-*d*<sub>6</sub>) δ ppm: 7.69/7.6 (dd, 2 H), 7.33-7.23 (m, 3 H), 7.16 (m, 2 H), 4.88 (t, 2 H), 4.31 (s, 2 H), 3.91 (t, 2 H), 3.53/3.43 (2m, 4 H), 2.7 (s, 3 H)

25

**STEP A6 : Preparation of ethyl (2*E*)-3-(1-{2-[2-(benzyloxy)ethoxy]ethyl}-4-methyl-1*H*-benzotriazol-5-yl)prop-2-enoate**

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Using General Procedure 1 STEP 7 starting from 1-{2-[2-(benzyloxy)ethoxy]ethyl}-5-bromo-4-methyl-1*H*-benzotriazole (1 eq., 3.65 g, 9.35 mmol) as a reactant, the title compound (1.7 g, 28% yield) was obtained.

5 <sup>1</sup>H-NMR (400 MHz, DMSO-d<sub>6</sub>) δ ppm: 8 (d, 1 H), 7.87 (d, 1 H), 7.72 (d, 1 H), 7.32-7.15 (m, 5 H), 6.6 (d, 1 H), 4.88 (t, 2 H), 4.32 (s, 2 H), 4.23 (q, 2 H), 3.92 (t, 2 H), 3.54/3.45 (2m, 4 H), 2.79 (s, 3 H), 1.29 (t, 3 H)

**STEP 1 : Preparation of ethyl 3-(1-{2-[2-(benzyloxy)ethoxy]ethyl}-4-methyl-1*H*-benzotriazol-5-yl)-3-{3-[(1*S*)-1-hydroxyethyl]-4-methylphenyl}propanoate**

10

Using General Procedure 6 starting from ethyl (2*E*)-3-(1-{2-[2-(benzyloxy)ethoxy]ethyl}-4-methyl-1*H*-benzotriazol-5-yl)prop-2-enoate (1 eq.) and (1*S*)-1-[2-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]ethan-1-ol (2 eq.) as reactants, the title compound (44% yield) was obtained.

15 <sup>1</sup>H-NMR (400 MHz, DMSO-d<sub>6</sub>) δ ppm: 7.61 (d, 1 H), 7.41 (d, 1 H), 7.4 (sl, 1 H), 7.32-7.18 (m, 5 H), 7.02 (dd, 1 H), 6.97 (d, 1 H), 4.98/4.97 (2d, 1 H), 4.85-4.78 (m, 4 H), 4.33/4.32 (2s, 2 H), 3.92 (q, 2 H), 3.89 (m, 2 H), 3.53/3.43 (2m, 4 H), 3.16-3.01 (m, 2 H), 2.75 (2s, 3 H), 2.18 (2s, 3 H), 1.22/1.2 (2d, 3 H), 1 (t, 3 H)

20 **STEP 2 : Preparation of ethyl 3-(3-{(1*R*)-1-[6-(benzyloxy)-2,2-dioxo-2*H*-1,2λ<sup>6</sup>,3-benzoxathiazin-3(4*H*)-yl]ethyl}-4-methylphenyl)-3-(1-{2-[2-(benzyloxy)ethoxy]ethyl}-4-methyl-1*H*-benzotriazol-5-yl)propanoate**

Using General Procedure 7 starting from ethyl 3-(1-{2-[2-(benzyloxy)ethoxy]ethyl}-4-methyl-1*H*-benzotriazol-5-yl)-3-{3-[(1*S*)-1-hydroxyethyl]-4-methylphenyl}propanoate (1 eq.) and 6-(benzyloxy)-3,4-dihydro-2*H*-1,2λ<sup>6</sup>,3-benzoxathiazine-2,2-dione (1.5 eq.) as reactants, the title compound (79% yield) was obtained.

25 <sup>1</sup>H-NMR (400 MHz, DMSO-d<sub>6</sub>) δ ppm: 7.62 (d, 1 H), 7.5 (d, 1 H), 7.48-7 (m, 13 H), 7.1-6.96 (m, 2 H), 6.89/6.83 (2d, 1 H), 5.26 (m, 1 H), 5.08 (m, 2 H), 4.86 (m, 1 H), 4.78 (m, 2 H), 4.41

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(s, 2 H), 4.28 (s, 2 H), 3.91 (q, 2 H), 3.88 (m, 2 H), 3.49/3.39 (2m, 4 H), 3.18 (m, 2 H), 2.76 (s, 3 H), 2.27 (s, 3 H), 1.4 (d, 3 H), 0.98 (t, 3 H)

**STEP 3 : Preparation of ethyl 3-{3-[(1*R*)-1-(6-hydroxy-2,2-dioxo-2*H*-1,2λ<sup>6</sup>,3-benzoxathiazin-3(4*H*)-yl)ethyl]-4-methylphenyl}-3-{1-[2-(2-hydroxyethoxy)ethyl]-4-methyl-1*H*-benzotriazol-5-yl}propanoate**

Using General Procedure 8 starting from ethyl 3-{3-[(1*R*)-1-[6-(benzyloxy)-2,2-dioxo-2*H*-1,2λ<sup>6</sup>,3-benzoxathiazin-3(4*H*)-yl)ethyl]-4-methylphenyl}-3-(1-[2-[2-(benzyloxy)ethoxy]ethyl]-4-methyl-1*H*-benzotriazol-5-yl)propanoate (1 eq.) as a reactant, the title compound (white solid, 94% yield) was obtained.

**<sup>1</sup>H-NMR** (400 MHz, DMSO-d<sub>6</sub>) δ ppm: 9.63 (m, 1 H), 7.65-7.53 (2dd, 2 H), 7.47 (m, 1 H), 7.14-7.08 (m, 2 H), 6.91 (2, 1 H), 6.76-6.7 (m, 1 H), 6.6/6.56 (2d, 1 H), 5.26 (q, 1 H), 4.88 (q, 1 H), 4.8 (t, 2 H), 4.37/4.31 (s+dd, 2 H), 3.95 (2q, 2 H), 3.89 (m, 2 H), 3.48-3.27 (m, 4 H), 3.22 (2d, 2 H), 2.77 (s, 3 H), 2.28 (s, 3 H), 1.43/1.41 (2d, 3 H), 1.02/1 (2t, 3 H)

**STEP 4 : Preparation of ethyl 3-{1-[2-(2-bromoethoxy)ethyl]-4-methyl-1*H*-benzotriazol-5-yl}-3-{3-[(1*R*)-1-(6-hydroxy-2,2-dioxo-2*H*-1,2λ<sup>6</sup>,3-benzoxathiazin-3(4*H*)-yl)ethyl]-4-methylphenyl}propanoate**

20

Using General Procedure 9 starting from ethyl 3-{3-[(1*R*)-1-(6-hydroxy-2,2-dioxo-2*H*-1,2λ<sup>6</sup>,3-benzoxathiazin-3(4*H*)-yl)ethyl]-4-methylphenyl}-3-{1-[2-(2-hydroxyethoxy)ethyl]-4-methyl-1*H*-benzotriazol-5-yl}propanoate (1 eq.) as a reactant, the title compound (71% yield) was obtained.

**<sup>1</sup>H-NMR** (400 MHz, DMSO-d<sub>6</sub>) δ ppm: 9.64 (m, 1 H), 7.67-7.55 (2dd, 2 H), 7.47 (m, 1 H), 7.14-7.08 (m, 2 H), 6.91 (m, 1 H), 6.76-6.7 (m, 1 H), 6.6/6.56 (2d, 1 H), 5.26 (q, 1 H), 4.88 (q, 1 H), 4.83 (t, 2 H), 4.36/4.31 (s+dd, 2 H), 3.95 (2q, 2 H), 3.93 (m, 2 H), 3.66 (m, 2 H), 3.44 (t, 2 H), 3.3/3.22 (2d, 2 H), 2.77 (s, 3 H), 2.28 (s, 3 H), 1.43/1.41 (2d, 3 H), 1.02/1 (2t, 3 H)

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**STEP 5 : Preparation of ethyl [(2*R*)-2,4,32-trimethyl-28,28-dioxo-19,22,27-trioxa-28 $\lambda^6$ -thia-1,14,15,16-tetraazahexacyclo[21.5.3.1<sup>3,7</sup>.1<sup>9,13</sup>.0<sup>12,16</sup>.0<sup>26,30</sup>]tritiaconta-3(33),4,6,9(32),10,12,14,23,25,30-decaen-8-yl]acetate**

5 Using General Procedure 11 starting from ethyl 3-{1-[2-(2-bromoethoxy)ethyl]-4-methyl-1*H*-benzotriazol-5-yl}-3-{3-[(1*R*)-1-(6-hydroxy-2,2-dioxo-2*H*-1,2 $\lambda^6$ ,3-benzoxathiazin-3(4*H*)-yl)ethyl]-4-methylphenyl}propanoate (1 eq.) as a reactant, the title compound (99% yield) was obtained.

10 <sup>1</sup>H-NMR (400 MHz, DMSO-d<sub>6</sub>)  $\delta$  ppm: 7.72/7.65 (2d, 1 H), 7.52/6.91 (2s, 1 H), 7.52/7.16 (2d, 1 H), 7.45/7.09 (2d, 1 H), 7.28/6.98 (2d, 1 H), 6.93/6.88 (2d, 1 H), 6.8/6.75 (2d, 1 H), 6.36/5.99 (2sl, 1 H), 5.4/5.26 (2m, 1 H), 4.93/4.85 (2m, 1 H), 4.83 (m, 2 H), 4.71/4.17/3.81 (2m, 2 H), 4.14-3.58 (m, 6 H), 4.03/3.93 (2q, 2 H), 3.23/2.96 (m+dd, 2 H), 2.81/2.8 (2s, 3 H), 2.33/2.29 (2s, 3 H), 1.53/1.42 (s+sl, 3 H), 1.17/1.02 (2m, 3 H)

15 **STEP 6 : Preparation of EXAMPLE 13**

Using General Procedure 12 starting from ethyl [(2*R*)-2,4,32-trimethyl-28,28-dioxo-19,22,27-trioxa-28 $\lambda^6$ -thia-1,14,15,16-tetraazahexacyclo[21.5.3.1<sup>3,7</sup>.1<sup>9,13</sup>.0<sup>12,16</sup>.0<sup>26,30</sup>]tritiaconta-3(33),4,6,9(32),10,12,14,23,25,30-decaen-8-yl]acetate (1 eq.) as a reactant, the title compound  
20 (white solid, 59% yield) was obtained.

The diastereo-pure final products or final intermediates were obtained by chromatographic separation on chiral column.

**Example 13a (2*R*,8*R*)**

25 **HRMS** calculated for C<sub>30</sub>H<sub>32</sub>N<sub>4</sub>O<sub>7</sub>S: 592.1992; [M+H]<sup>+</sup> found: 593.2072 ( $\delta$ =1.3 ppm)

<sup>1</sup>H-NMR (400 MHz, DMSO-d<sub>6</sub>)  $\delta$  ppm: 13.6-11 (m, 1 H), 7.64 (d, 1 H), 7.48 (dd, 1 H), 7.27 (d, 1 H), 7.11 (d, 1 H), 6.94 (d, 1 H), 6.88 (sl, 1 H), 6.8 (dd, 1 H), 6.01 (d, 1 H), 5.24 (q, 1 H), 4.92 (t, 1 H), 4.81 (t, 2 H), 4.14/3.78 (dd, 2 H), 4.1/4.04 (2m, 2 H), 3.99-3.63 (m, 4 H), 3.06/2.75 (2dd, 2 H), 2.79 (s, 3 H), 2.33 (s, 3 H), 1.15 (d, 3 H)

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**Example 13b (2R,8S)**

**HRMS** calculated for  $C_{30}H_{32}N_4O_7S$ : 592.1992;  $[M+H]^+$  found: 593.2071 ( $\delta=1.1$  ppm)

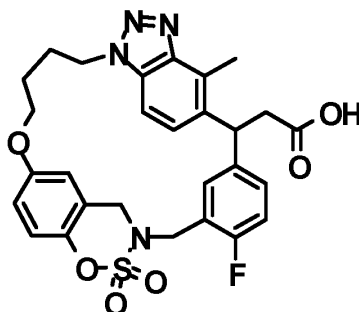
**$^1H$ -NMR** (400 MHz, DMSO- $d_6$ )  $\delta$  ppm: 13.6-11 (m, 1 H), 7.71 (d, 1 H), 7.51 (d, 1 H), 7.49 (d, 1 H), 7.1 (dd, 1 H), 6.99 (d, 1 H), 6.89 (d, 1 H), 6.76 (dd, 1 H), 6.33 (d, 1 H), 5.37 (q, 1 H),  
 5 4.88-4.77 (m, 3 H), 4.64/4.13 (dd, 2 H), 3.96 (m, 2 H), 3.96-3.58 (m, 4 H), 3.08 (d, 2 H), 2.79 (s, 3 H), 2.28 (s, 3 H), 1.49 (d, 3 H)

Preparation of the sodium salt:

The compound of Example 13b (2.03g) and sodium hydroxide (0.14g) were suspended in  
 10 water (235mL) at 25°C. Tert-butanol (100mL) was added to the suspension and the reaction mixture was heated at 60°C for at least 1 hour (until complete dissolution). The solution was then cooled to -20°C for fast solidification before the lyophilization step for 96 hours. After isolation from the lyophilization vessel, 2.10g of the amorphous sodium salt of [(2R,8S)-2,4,32-trimethyl-28,28-dioxo-19,22,27-trioxa-28 $\lambda^6$ -thia-1,14,15,16-tetraazahexacyclo  
 15 [21.5.3.1<sup>3,7</sup>.1<sup>9,13</sup>.0<sup>12,16</sup>.0<sup>26,30</sup>]tritiaconta-3(33),4,6,9(32),10,12,14,23,25,30-decaen-8-yl]acetic acid (water content: 3.0%) were obtained.

**IR**: 2980 to 2860  $cm^{-1}$  ( $CH_2$ ,  $CH_3$ ), 1574  $cm^{-1}$  ( $COO^-$  asym), 1492  $cm^{-1}$  ( $C=C$ ), 1391  $cm^{-1}$  ( $COO^-$  sym and  $SO_2$  asym), 1200 to 1130  $cm^{-1}$  ( $SO_2$  sym,  $=C-O-C$  asym and  $C-O-C$  asym).

20 **EXAMPLE 14** : [4-Fluoro-31-methyl-27,27-dioxo-21,26-dioxa-27 $\lambda^6$ -thia-1,14,15,16-tetraazahexacyclo[20.5.3.1<sup>3,7</sup>.1<sup>9,13</sup>.0<sup>12,16</sup>.0<sup>25,29</sup>]dotriaconta-3(32),4,6,9(31),10,12,14,22,24,29-decaen-8-yl]acetic acid





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**STEP 1 : Preparation of ethyl 3-(3-{[6-(benzyloxy)-2,2-dioxo-2*H*-1,2λ<sup>6</sup>,3-benzoxathiazin-3(4*H*)-yl]methyl}-4-fluorophenyl)-3-(1-{4-[(4-methoxyphenyl)methoxy]butyl}-4-methyl-1*H*-benzotriazol-5-yl)propanoate**

5 Using General Procedure 6 starting from ethyl (E)-3-[1-[4-[(4-methoxyphenyl)methoxy]butyl]-4-methyl-benzotriazol-5-yl]prop-2-enoate (1 eq.) and [2-fluoro-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]methanol (1 eq.) as reactants, ethyl 3-[4-fluoro-3-(hydroxymethyl)phenyl]-3-(1-{4-[(4-methoxyphenyl)methoxy]butyl}-4-methyl-1*H*-benzotriazol-5-yl)propanoate (17% yield) was obtained. The crude product was reacted using  
10 General Procedure 7 with 6-(benzyloxy)-3,4-dihydro-2*H*-1,2λ<sup>6</sup>,3-benzoxathiazine-2,2-dione (1.1 eq.) resulting the title compound (85% yield).

<sup>1</sup>H-NMR (400 MHz, DMSO-d<sub>6</sub>) δ ppm: 7.6 (d, 1 H), 7.5-7.35 (m, 5 H), 7.49 (d, 1 H), 7.35/7.3 (m, 2 H), 7.2 (d, 2 H), 7.08 (t, 1 H), 7-6.95 (m, 3 H), 6.88 (d, 2 H), 5.08 (s, 2 H), 4.88 (t, 1 H), 4.65 (t, 2 H), 4.58 (s, 2 H), 4.31 (2s, 4 H), 3.92 (q, 2 H), 3.71 (s, 3 H), 3.38 (t, 2 H), 3.18 (d, 2  
15 H), 2.79 (s, 3 H), 1.91 (m, 2 H), 1.48 (m, 2 H), 1 (t, 3 H)

**STEP 2 : Preparation of ethyl 3-{4-fluoro-3-[(6-hydroxy-2,2-dioxo-2*H*-1,2λ<sup>6</sup>,3-benzoxathiazin-3(4*H*)-yl)methyl]phenyl}-3-[1-(4-hydroxybutyl)-4-methyl-1*H*-benzotriazol-5-yl]propanoate**

20

Using General Procedure 8 starting from ethyl 3-(3-{[6-(benzyloxy)-2,2-dioxo-2*H*-1,2λ<sup>6</sup>,3-benzoxathiazin-3(4*H*)-yl]methyl}-4-fluorophenyl)-3-(1-{4-[(4-methoxyphenyl)methoxy]butyl}-4-methyl-1*H*-benzotriazol-5-yl)propanoate (1 eq.) as a reactant, the title compound (white solid, 77% yield) was obtained.

25 <sup>1</sup>H-NMR (400 MHz, DMSO-d<sub>6</sub>) δ ppm: 9.4/4.4 (s+t, 2 H), 7.63 (d, 1 H), 7.5 (d, 1 H), 7.45 (dd, 1 H), 7.3 (m, 1 H), 7.1 (t, 1 H), 6.88 (d, 1 H), 6.71 (dd, 1 H), 6.61 (d, 1 H), 4.88 (t, 1 H), 4.67 (t, 2 H), 4.53 (s, 2 H), 4.3 (s, 2 H), 3.95 (q, 2 H), 3.4 (q, 2 H), 3.2 (d, 2 H), 2.78 (s, 3 H), 1.9 (m, 2 H), 1.38 (m, 2 H), 1.02 (t, 3 H)

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**STEP 3 : Preparation of ethyl 3-[1-(4-bromobutyl)-4-methyl-1*H*-benzotriazol-5-yl]-3-{4-fluoro-3-[(6-hydroxy-2,2-dioxo-2*H*-1,2λ<sup>6</sup>,3-benzoxathiazin-3(4*H*)-yl)methyl]phenyl}propanoate**

5 Using General Procedure 9 starting from ethyl 3-{4-fluoro-3-[(6-hydroxy-2,2-dioxo-2*H*-1,2λ<sup>6</sup>,3-benzoxathiazin-3(4*H*)-yl)methyl]phenyl}-3-[1-(4-hydroxybutyl)-4-methyl-1*H*-benzotriazol-5-yl]propanoate (1 eq.) as a reactant, the title compound (31% yield) was obtained. <sup>1</sup>H-NMR (400 MHz, DMSO-d<sub>6</sub>) δ ppm: 9.6 (s, 1 H), 7.65 (d, 1 H), 7.51 (d, 1 H), 7.45 (dd, 1 H), 7.3 (m, 1 H), 7.1 (t, 1 H), 6.88 (d, 1 H), 6.71 (dd, 1 H), 6.6 (d, 1 H), 4.88 (t, 1 H), 4.7 (t, 2 H), 4.52 (s, 2 H), 4.31 (s, 2 H), 3.93 (q, 2 H), 3.55 (t, 2 H), 3.2 (d, 2 H), 2.79 (s, 3 H), 2 (m, 2 H), 1.8 (m, 2 H), 1 (t, 3 H)

**STEP 4 : Preparation of ethyl [4-fluoro-31-methyl-27,27-dioxo-21,26-dioxa-27λ<sup>6</sup>-thia-1,14,15,16-tetraazahexacyclo[20.5.3.1<sup>3,7</sup>.1<sup>9,13</sup>.0<sup>12,16</sup>.0<sup>25,29</sup>]dotriaconta-3(32),4,6,9(31),10,12,14,22,24,29-decaen-8-yl]acetate**

Using General Procedure 11 starting from ethyl 3-[1-(4-bromobutyl)-4-methyl-1*H*-benzotriazol-5-yl]-3-{4-fluoro-3-[(6-hydroxy-2,2-dioxo-2*H*-1,2λ<sup>6</sup>,3-benzoxathiazin-3(4*H*)-yl)methyl]phenyl} propanoate (1 eq.) as a reactant, the title compound (white solid, 75% yield) was obtained. <sup>1</sup>H-NMR (400 MHz, DMSO-d<sub>6</sub>) δ ppm: 7.7 (d, 1 H), 7.61 (dd, 1 H), 7.45 (d, 1 H), 7.29 (t, 1 H), 6.98 (d, 1 H), 6.81 (dd, 1 H), 6.78 (dd, 1 H), 6.4 (d, 1 H), 4.85-4.7 (m, 3 H), 4.21/4.05 (2d, 2 H), 4.02/3.92 (2d, 2 H), 3.95 (q, 2 H), 3.68/3.42 (2m, 2 H), 3.2/3.1 (2dd, 2 H), 2.65 (s, 3 H), 2.2/2.02 (2m, 2 H), 1.8/1.65 (2m, 2 H), 1.01 (t, 3 H)

25

**STEP 5 : Preparation of EXAMPLE 14**

Using General Procedure 12 starting from ethyl [4-fluoro-31-methyl-27,27-dioxo-21,26-dioxa-27λ<sup>6</sup>-thia-1,14,15,16-tetraazahexacyclo[20.5.3.1<sup>3,7</sup>.1<sup>9,13</sup>.0<sup>12,16</sup>.0<sup>25,29</sup>]dotriaconta-

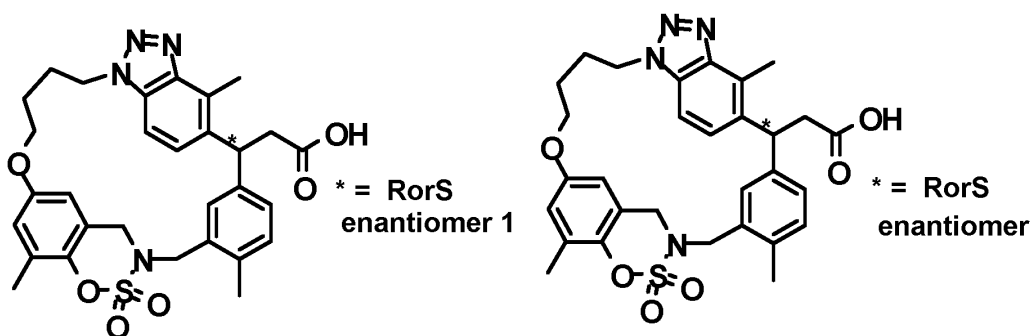
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3(32),4,6,9(31),10,12,14,22,24,29-decaen-8-yl]acetate (1 eq.) as a reactant, the title compound (white solid, 81% yield) was obtained.

**HRMS** calculated for  $C_{28}H_{27}FN_4O_6S$ : 566.1635;  $[M+H]^+$  found: 567.1712 ( $\delta=0.7$  ppm)

**$^1H$ -NMR** (400 MHz, DMSO- $d_6$ )  $\delta$  ppm: 12.3 (m, 1 H), 7.67 (d, 1 H), 7.63 (m, 1 H), 7.42 (d, 1 H), 7.27 (t, 1 H), 6.97 (d, 1 H), 6.76 (m, 1 H), 6.76 (m, 1 H), 5.88 (d, 1 H), 4.8 (t, 2 H), 4.77 (m, 1 H), 4.21/4.05 (dd, 2 H), 4.06/3.92 (dd, 2 H), 3.66/3.4 (2m, 2 H), 3.06/2.95 (2dd, 2 H), 2.65 (s, 3 H), 2.21/2.05 (2m, 2 H), 1.79/1.59 (2m, 2 H)

**EXAMPLE 15** : [4,24,31-Trimethyl-27,27-dioxo-21,26-dioxa-27 $\lambda^6$ -thia-1,14,15,16-tetraazahexacyclo[20.5.3.1<sup>3,7</sup>.1<sup>9,13</sup>.0<sup>12,16</sup>.0<sup>25,29</sup>]dotriaconta-3(32),4,6,9(31),10,12,14,22,24,29-decaen-8-yl]acetic acid



#### 15 STEP C1 : Preparation of 6-bromo-8-methyl-2*H*-1,2 $\lambda^6$ ,3-benzoxathiazine-2,2-dione

Using General Procedure 4 STEP 2 starting from 5-bromo-2-hydroxy-3-methylbenzaldehyde (1 eq., 3.65 g, 9.35 mmol) as a reactant, the title compound (2.85 g, 30% yield) was obtained.

**$^1H$ -NMR** (400 MHz, DMSO- $d_6$ )  $\delta$  ppm: 9.14 (sl, 1 H), 8.09/8.05 (dl+dd, 2 H), 2.33 (s, 3 H)

20

#### STEP C2 : Preparation of 6-bromo-8-methyl-3,4-dihydro-2*H*-1,2 $\lambda^6$ ,3-benzoxathiazine-2,2-dione

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Using General Procedure 4 STEP 3 starting from 6-bromo-8-methyl-2*H*-1,2λ<sup>6</sup>,3-benzoxathiazine-2,2-dione (1 eq., 4.52 g, 16.37 mmol) as a reactant, the title compound (4.64 g, 99% yield) was obtained.

<sup>1</sup>H-NMR (400 MHz, DMSO-d<sub>6</sub>) δ ppm: 8.59 (t, 1 H), 7.5/7.38 (2d, 2 H), 4.55 (sl, 2 H), 2.2 (s, 3 H)

**STEP C3 : Preparation of *tert*-butyl 6-bromo-8-methyl-2,2-dioxo-2*H*-1,2λ<sup>6</sup>,3-benzoxathiazine-3(4*H*)-carboxylate**

Using General Procedure 5 STEP 1 starting from 6-bromo-8-methyl-3,4-dihydro-2*H*-1,2λ<sup>6</sup>,3-benzoxathiazine-2,2-dione (1 eq., 4.6 g, 16.539 mmol) as a reactant, the title compound (6.2 g, 99% yield) was obtained.

<sup>1</sup>H-NMR (400 MHz, DMSO-d<sub>6</sub>) δ ppm: 7.7/7.64 (2d, 2 H), 5.04 (s, 2 H), 2.27 (s, 3 H), 1.48 (s, 9 H)

**STEP C4 : Preparation of *tert*-butyl 8-methyl-2,2-dioxo-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2*H*-1,2λ<sup>6</sup>,3-benzoxathiazine-3(4*H*)-carboxylate**

Using General Procedure 5 STEP 2 starting from *tert*-butyl 6-bromo-8-methyl-2,2-dioxo-2*H*-1,2λ<sup>6</sup>,3-benzoxathiazine-3(4*H*)-carboxylate (1 eq., 6.2 g, 16.39 mmol) as a reactant, the title compound (4.9 g, 70% yield) was obtained.

<sup>1</sup>H-NMR (400 MHz, DMSO-d<sub>6</sub>) δ ppm: 7.69/7.65 (2sl, 2 H), 5.06 (s, 2 H), 2.29 (s, 3 H), 1.48 (s, 9 H), 1.3 (s, 12 H)

**STEP C5 : Preparation of *tert*-butyl 6-hydroxy-8-methyl-2,2-dioxo-2*H*-1,2λ<sup>6</sup>,3-benzoxathiazine-3(4*H*)-carboxylate**

Using General Procedure 5 STEP 3 starting from *tert*-butyl 8-methyl-2,2-dioxo-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2*H*-1,2λ<sup>6</sup>,3-benzoxathiazine-3(4*H*)-carboxylate (1 eq., 4.9 g, 11.52 mmol) as a reactant, the title compound (3.9 g, 97% yield) was obtained.

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<sup>1</sup>H-NMR (400 MHz, DMSO-d<sub>6</sub>) δ ppm: 9.81 (m, 1 H), 6.74/6.7 (2d, 2 H), 4.9 (s, 2 H), 2.19 (s, 3 H), 1.48 (s, 9 H)

**STEP C6 : Preparation of *tert*-butyl 6-(benzyloxy)-8-methyl-2,2-dioxo-2*H*-1,2λ<sup>6</sup>,3-benzoxathiazine-3(4*H*)-carboxylate**

Using General Procedure 5 STEP 4 starting from *tert*-butyl 6-hydroxy-8-methyl-2,2-dioxo-2*H*-1,2λ<sup>6</sup>,3-benzoxathiazine-3(4*H*)-carboxylate (1 eq., 2.9 g, 9.19 mmol) as a reactant, the title compound (5 g, quant.) was obtained.

<sup>1</sup>H-NMR (400 MHz, DMSO-d<sub>6</sub>) δ ppm: 7.46-7.29 (m, 5 H), 7.12/7.03 (2d, 2 H), 5.1 (s, 2 H), 4.97 (s, 2 H), 2.26 (s, 3 H), 1.48 (s, 9 H)

**STEP C7 : Preparation of 6-(benzyloxy)-8-methyl-3,4-dihydro-2*H*-1,2λ<sup>6</sup>,3-benzoxathiazine-2,2-dione**

Using General Procedure 5 STEP 5 starting from *tert*-butyl 6-(benzyloxy)-8-methyl-2,2-dioxo-2*H*-1,2λ<sup>6</sup>,3-benzoxathiazine-3(4*H*)-carboxylate (1 eq., 5.0 g, 12.33 mmol) as a reactant, the title compound (1.85 g, 65% yield) was obtained.

<sup>1</sup>H-NMR (400 MHz, DMSO-d<sub>6</sub>) δ ppm: 8.37 (m, 1 H), 7.46-7.3 (m, 5 H), 6.92/6.79 (2d, 2 H), 5.06 (s, 2 H), 4.47 (s, 2 H), 2.16 (s, 3 H)

**STEP 1 : Preparation of ethyl 3-[3-(hydroxymethyl)-4-methylphenyl]-3-(1-{4-[(4-methoxyphenyl)methoxy]butyl}-4-methyl-1*H*-benzotriazol-5-yl)propanoate**

Using General Procedure 6 starting from ethyl (E)-3-[1-[4-[(4-methoxyphenyl)methoxy]butyl]-4-methyl-benzotriazol-5-yl]prop-2-enoate (1 eq.) and [2-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]methanol (2 eq.) as reactants, the title compound (43% yield) was obtained.

<sup>1</sup>H-NMR (400 MHz, DMSO-d<sub>6</sub>) δ ppm: 7.58 (d, 1 H), 7.45 (d, 1 H), 7.28 (d, 1 H), 7.2 (d, 2 H), 7.1 (dd, 1 H), 7.01 (d, 1 H), 6.88 (d, 2 H), 4.98 (t, 1 H), 4.82 (t, 1 H), 4.65 (t, 2 H), 4.4 (d,

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2 H), 4.3 (s, 2 H), 3.91 (q, 2 H), 3.71 (s, 3 H), 3.4 (t, 2 H), 3.11 (dd, 2 H), 2.75 (s, 3 H), 2.15 (s, 3 H), 1.91 (m, 2 H), 1.48 (m, 2 H), 1 (t, 3 H)

**STEP 2 : Preparation of ethyl 3-(3-{[6-(benzyloxy)-8-methyl-2,2-dioxo-2*H*-1,2λ<sup>6</sup>,3-benzoxathiazin-3(4*H*)-yl]methyl}-4-methylphenyl)-3-(1-{4-[(4-methoxyphenyl)methoxy]butyl}-4-methyl-1*H*-benzotriazol-5-yl)propanoate**

Using General Procedure 7 starting from ethyl 3-[3-(hydroxymethyl)-4-methylphenyl]-3-(1-{4-[(4-methoxyphenyl)methoxy]butyl}-4-methyl-1*H*-benzotriazol-5-yl)propanoate (1 eq.) and 6-(benzyloxy)-8-methyl-3,4-dihydro-2*H*-1,2λ<sup>6</sup>,3-benzoxathiazine-2,2-dione (1.5 eq.) as reactants, the title compound (88% yield) was obtained.

**<sup>1</sup>H-NMR** (400 MHz, DMSO-d<sub>6</sub>) δ ppm: 7.56 (d, 1 H), 7.47 (d, 1 H), 7.46-7.31 (m, 5 H), 7.46-7.12 (m, 3 H), 7.19 (d, 2 H), 7/6.75 (2d, 2 H), 6.86 (d, 2 H), 5.08 (s, 2 H), 4.85 (t, 1 H), 4.6 (t, 2 H), 4.38 (s, 2 H), 4.23 (s, 2 H), 4.21 (s, 2 H), 3.92 (q, 2 H), 3.72 (s, 3 H), 3.35 (t, 2 H), 3.16 (m, 2 H), 2.76 (s, 3 H), 2.22/2.21 (2s, 6 H), 1.89 (m, 2 H), 1.44 (m, 2 H), 0.97 (t, 3 H)

**STEP 3 : Preparation of ethyl 3-[1-(4-hydroxybutyl)-4-methyl-1*H*-benzotriazol-5-yl]-3-{3-[(6-hydroxy-8-methyl-2,2-dioxo-2*H*-1,2λ<sup>6</sup>,3-benzoxathiazin-3(4*H*)-yl)methyl]-4-methylphenyl}propanoate**

20

Using General Procedure 8 starting from ethyl 3-(3-{[6-(benzyloxy)-8-methyl-2,2-dioxo-2*H*-1,2λ<sup>6</sup>,3-benzoxathiazin-3(4*H*)-yl]methyl}-4-methylphenyl)-3-(1-{4-[(4-methoxyphenyl)methoxy]butyl}-4-methyl-1*H*-benzotriazol-5-yl)propanoate (1 eq.) as a reactant, the title compound (white solid, 97% yield) was obtained.

**<sup>1</sup>H-NMR** (400 MHz, DMSO-d<sub>6</sub>) δ ppm: 9.55 (m, 1 H), 7.61 (d, 1 H), 7.49 (d, 1 H), 7.22-7.11 (3m, 3 H), 6.68/6.42 (2d, 2 H), 4.84 (t, 1 H), 4.65 (t, 2 H), 4.34 (s, 2 H), 4.19 (dd, 2 H), 3.94 (q, 2 H), 3.38 (t, 2 H), 3.18/3.13 (2dd, 2 H), 2.75 (s, 3 H), 2.22/2.17 (2s, 6 H), 1.9 (m, 2 H), 1.36 (m, 2 H), 1 (t, 3 H)

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**STEP 4 : Preparation of ethyl 3-[1-(4-bromobutyl)-4-methyl-1*H*-benzotriazol-5-yl]-3-{3-[(6-hydroxy-8-methyl-2,2-dioxo-2*H*-1,2λ<sup>6</sup>,3-benzoxathiazin-3(4*H*)-yl)methyl]-4-methylphenyl}propanoate**

5 Using General Procedure 9 starting from ethyl 3-[1-(4-hydroxybutyl)-4-methyl-1*H*-benzotriazol-5-yl]-3-{3-[(6-hydroxy-8-methyl-2,2-dioxo-2*H*-1,2λ<sup>6</sup>,3-benzoxathiazin-3(4*H*)-yl)methyl]-4-methylphenyl}propanoate (1 eq.) as a reactant, the title compound (78% yield) was obtained.

<sup>1</sup>**H-NMR** (400 MHz, DMSO-d<sub>6</sub>) δ ppm: 9.55 (s, 1 H), 7.65 (d, 1 H), 7.5 (d, 1 H), 7.2 (m, 2 H),  
 10 7.11 (d, 1 H), 6.7/6.41 (2d, 2 H), 4.85 (t, 1 H), 4.7 (t, 2 H), 4.38 (s, 2 H), 4.2 (m, 2 H), 3.95 (q, 2 H), 3.55 (t, 2 H), 3.18 (m, 2 H), 2.78 (s, 3 H), 2.22/2.18 (2s, 6 H), 1.98 (m, 2 H), 1.78 (m, 2 H), 1 (t, 3 H)

**STEP 5 : Preparation of ethyl [4,24,31-trimethyl-27,27-dioxo-21,26-dioxa-27λ<sup>6</sup>-thia-1,14,15,16-tetraazahexacyclo[20.5.3.1<sup>3,7</sup>.1<sup>9,13</sup>.0<sup>12,16</sup>.0<sup>25,29</sup>]dotriaconta-3(32),4,6,9(31),10,12,14,22,24,29-decaen-8-yl]acetate**

Using General Procedure 11 starting from ethyl 3-[1-(4-bromobutyl)-4-methyl-1*H*-benzotriazol-5-yl]-3-{3-[(6-hydroxy-8-methyl-2,2-dioxo-2*H*-1,2λ<sup>6</sup>,3-benzoxathiazin-3(4*H*)-yl)methyl]-4-methylphenyl}propanoate (1 eq.) as a reactant, the title compound (quant.) was  
 20 obtained.

<sup>1</sup>**H-NMR** (400 MHz, DMSO-d<sub>6</sub>) δ ppm: 7.67 (d, 1 H), 7.47 (dd, 1 H), 7.43 (d, 1 H), 7.43 (d, 1 H), 6.71 (d, 1 H), 6.55 (d, 1 H), 5.67 (d, 1 H), 4.84-4.7 (m, 3 H), 4.13-3.79 (2dd, 4 H), 3.92 (q, 2 H), 3.63-3.43 (2m, 2 H), 3.17/3.04 (2dd, 2 H), 2.63 (s, 3 H), 2.33 (s, 3 H), 2.25-2 (m, 2 H),  
 25 2.11 (s, 3 H), 1.79/1.6 (2m, 2 H), 1 (t, 3 H)

**STEP 6 : Preparation of EXAMPLE 15**

Using General Procedure 12 starting from ethyl [4,24,31-trimethyl-27,27-dioxo-21,26-dioxa-27λ<sup>6</sup>-thia-1,14,15,16-tetraazahexacyclo[20.5.3.1<sup>3,7</sup>.1<sup>9,13</sup>.0<sup>12,16</sup>.0<sup>25,29</sup>]dotriaconta-

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3(32),4,6,9(31),10,12,14,22,24,29-decaen-8-yl]acetate (1 eq.) as a reactant, the title compound (white solid, 66% yield) was obtained.

The enantiopure products were obtained by chromatographic separation on chiral column.

#### 5 **Example 15a (E1)**

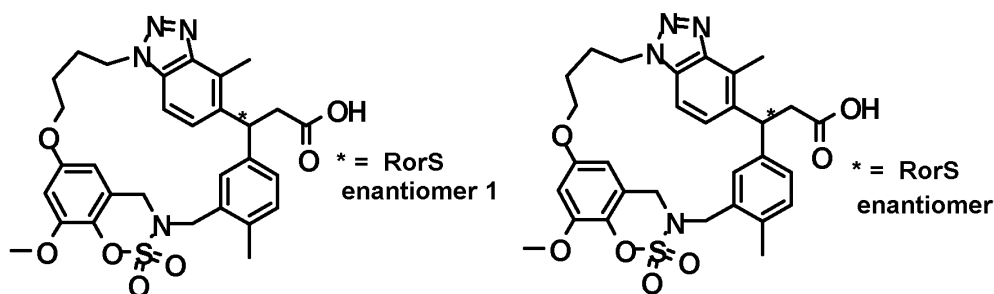
**HRMS** calculated for  $C_{30}H_{32}N_4O_6S$ : 576.2042;  $[M+H]^+$  found: 577.2119 ( $\delta=0.6$  ppm)

#### **Example 15b (E2)**

**HRMS** calculated for  $C_{30}H_{32}N_4O_6S$ : 576.2042;  $[M+H]^+$  found: 577.2117 ( $\delta=0.3$  ppm)

10  **$^1H$ -NMR** (400 MHz, DMSO- $d_6$ )  $\delta$  ppm: 12.14 (m, 1 H), 7.67 (d, 1 H), 7.49 (dd, 1 H), 7.42 (d, 1 H), 7.29 (d, 1 H), 6.71 (d, 1 H), 6.53 (d, 1 H), 5.66 (d, 1 H), 4.84-4.7 (m, 3 H), 4.13-3.79 (2dd, 4 H), 3.63-3.43 (2m, 2 H), 3.07/2.94 (2dd, 2 H), 2.63 (s, 3 H), 2.33 (s, 3 H), 2.19/2.08 (2m, 2 H), 2.11 (s, 3 H), 1.8/1.6 (2m, 2 H)

15 **EXAMPLE 16** : [24-Methoxy-4,31-dimethyl-27,27-dioxo-21,26-dioxa-27 $\lambda^6$ -thia-1,14,15,16-tetraazahexacyclo[20.5.3.1<sup>3,7</sup>.1<sup>9,13</sup>.0<sup>12,16</sup>.0<sup>25,29</sup>]dotriaconta-3(32),4,6,9(31),10,12,14,22,24,29-decaen-8-yl]acetic acid



20

#### **STEP C1 : Preparation of 6-bromo-8-methoxy-2H-1,2 $\lambda^6$ ,3-benzoxathiazine-2,2-dione**

Using General Procedure 4 STEP 2 starting from 5-bromo-2-hydroxy-3-methoxy-benzaldehyde (1 eq.) as a reactant, the title compound (32% yield) was obtained.



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<sup>1</sup>H-NMR (400 MHz, DMSO-d<sub>6</sub>) δ ppm: 9.14 (s, 1 H), 7.83/7.79 (2d, 2 H), 3.98 (s, 3 H)

**STEP C2 : Preparation of 6-bromo-8-methoxy-3,4-dihydro-2H-1,2λ<sup>6</sup>,3-benzoxathiazine-2,2-dione**

5

Using General Procedure 4 STEP 3 starting from 6-bromo-8-methoxy-2H-1,2λ<sup>6</sup>,3-benzoxathiazine-2,2-dione (1 eq.) as a reactant, the title compound (95% yield) was obtained.

<sup>1</sup>H-NMR (400 MHz, DMSO-d<sub>6</sub>) δ ppm: 8.6 (sl, 1 H), 7.26 (d, 1 H), 7.1 (d, 1 H), 4.55 (s, 2 H), 3.85 (s, 3 H)

10

**STEP C3 : Preparation of *tert*-butyl 6-bromo-8-methoxy-2,2-dioxo-2H-1,2λ<sup>6</sup>,3-benzoxathiazine-3(4H)-carboxylate**

Using General Procedure 5 STEP 1 starting from 6-bromo-8-methoxy-3,4-dihydro-2H-1,2λ<sup>6</sup>,3-benzoxathiazine-2,2-dione (1 eq.) as a reactant, the title compound (88% yield) was obtained.

15

<sup>1</sup>H-NMR (400 MHz, DMSO-d<sub>6</sub>) δ ppm: 7.48 (s, 1 H), 7.4 (s, 1 H), 5.05 (s, 2 H), 3.9 (s, 3 H), 1.5 (s, 9 H)

20

**STEP C4 : Preparation of *tert*-butyl 8-methoxy-2,2-dioxo-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2H-1,2λ<sup>6</sup>,3-benzoxathiazine-3(4H)-carboxylate**

Using General Procedure 5 STEP 2 starting from *tert*-butyl 6-bromo-8-methoxy-2,2-dioxo-2H-1,2λ<sup>6</sup>,3-benzoxathiazine-3(4H)-carboxylate (1 eq.) as a reactant, the title compound (80% yield) was obtained.

25

<sup>1</sup>H-NMR (400 MHz, DMSO-d<sub>6</sub>) δ ppm: 7.41 (d, 1 H), 7.31 (d, 1 H), 5.09 (s, 2 H), 3.9 (s, 3 H), 1.49 (s, 9 H), 1.3 (s, 12 H)

**STEP C5 : Preparation of *tert*-butyl 6-hydroxy-8-methoxy-2,2-dioxo-2H-1,2λ<sup>6</sup>,3-benzoxathiazine-3(4H)-carboxylate**

30

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Using General Procedure 5 STEP 3 starting from *tert*-butyl 8-methoxy-2,2-dioxo-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2*H*-1,2λ<sup>6</sup>,3-benzoxathiazine-3(4*H*)-carboxylate (1 eq.) as a reactant, the title compound (81% yield) was obtained.

<sup>1</sup>H-NMR (400 MHz, DMSO-d<sub>6</sub>) δ ppm: 9.92 (m, 1 H), 6.52 (d, 1 H), 6.43 (d, 1 H), 4.9 (s, 2 H),  
5 3.8 (s, 3 H), 1.48 (s, 9 H)

**STEP C6 : Preparation of *tert*-butyl 6-(benzyloxy)-8-methoxy-2,2-dioxo-2*H*-1,2λ<sup>6</sup>,3-benzoxathiazine-3(4*H*)-carboxylate**

10 Using General Procedure 5 STEP 4 starting from *tert*-butyl 6-hydroxy-8-methoxy-2,2-dioxo-2*H*-1,2λ<sup>6</sup>,3-benzoxathiazine-3(4*H*)-carboxylate (1 eq.) as a reactant, the title compound (74% yield) was obtained.

<sup>1</sup>H-NMR (400 MHz, DMSO-d<sub>6</sub>) δ ppm: 7.5-7.28 (m, 5 H), 6.83 (sl, 2 H), 5.12 (s, 2 H), 4.98 (s,  
15 2 H), 3.86 (s, 3 H), 1.5 (s, 9 H)

**STEP C7 : Preparation of 6-(benzyloxy)-8-methoxy-3,4-dihydro-2*H*-1,2λ<sup>6</sup>,3-benzoxathiazine-2,2-dione**

Using General Procedure 5 STEP 5 starting from *tert*-butyl 6-(benzyloxy)-8-methoxy-2,2-dioxo-2*H*-1,2λ<sup>6</sup>,3-benzoxathiazine-3(4*H*)-carboxylate (1 eq.) as a reactant, the title compound (89% yield) was obtained.

<sup>1</sup>H-NMR (400 MHz, DMSO-d<sub>6</sub>) δ ppm: 8.4 (sl, 1 H), 7.48-7.3 (m, 5 H), 6.71 (d, 1 H), 6.5 (d,  
20 1 H), 5.08 (s, 2 H), 4.49 (s, 2 H), 3.8 (s, 3 H)

25 **STEP 1 : Preparation of ethyl 3-(3-{[6-(benzyloxy)-8-methoxy-2,2-dioxo-2*H*-1,2λ<sup>6</sup>,3-benzoxathiazin-3(4*H*)-yl]methyl}-4-methylphenyl)-3-(1-{4-[(4-methoxyphenyl)methoxy]butyl}-4-methyl-1*H*-benzotriazol-5-yl)propanoate**

Using General Procedure 7 starting from ethyl 3-[3-(hydroxymethyl)-4-methylphenyl]-3-(1-{4-  
30 [(4-methoxyphenyl)methoxy]butyl}-4-methyl-1*H*-benzotriazol-5-yl)propanoate (1 eq.) and 6-

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(benzyloxy)-8-methoxy-3,4-dihydro-2*H*-1,2λ<sup>6</sup>,3-benzoxathiazine-2,2-dione (1.2 eq.) as reactants, the title compound (yellow solid, 88% yield) was obtained.

<sup>1</sup>H-NMR (400 MHz, DMSO-d<sub>6</sub>) δ ppm: 7.57 (d, 1 H), 7.48 (d, 2 H), 7.48 (d, 1 H), 7.4 (t, 2 H), 7.33 (t, 1 H), 7.22-7.1 (m, 5 H), 6.87 (d, 2 H), 6.8 (d, 1 H), 6.47 (d, 1 H), 5.09 (s, 2 H),  
5 4.83 (t, 1 H), 4.6 (t, 2 H), 4.39 (s, 2 H), 4.29 (s, 2 H), 4.2 (s, 2 H), 3.9 (q, 2 H), 3.82 (s, 3 H),  
3.7 (s, 3 H), 3.33 (t, 2 H), 3.18 (m, 2 H), 2.73 (s, 3 H), 2.2 (s, 3 H), 1.89 (m, 2 H), 1.42 (m, 2 H), 0.98 (t, 3 H)

**STEP 2 : Preparation of ethyl 3-[1-(4-hydroxybutyl)-4-methyl-1*H*-benzotriazol-5-yl]-3-  
10 {3-[(6-hydroxy-8-methoxy-2,2-dioxo-2*H*-1,2λ<sup>6</sup>,3-benzoxathiazin-3(4*H*)-  
yl)methyl]-4-methylphenyl}propanoate**

Using General Procedure 8 starting from ethyl 3-(3-{[6-(benzyloxy)-8-methoxy-2,2-dioxo-2*H*-  
1,2λ<sup>6</sup>,3-benzoxathiazin-3(4*H*)-yl]methyl}-4-methylphenyl)-3-(1-{4-[(4-methoxyphenyl)  
15 methoxy]butyl}-4-methyl-1*H*-benzotriazol-5-yl)propanoate (1 eq.) as a reactant, the title  
compound (white solid, 97% yield) was obtained.

<sup>1</sup>H-NMR (400 MHz, DMSO-d<sub>6</sub>) δ ppm: 9.7/4.41 (s+t, 2 H), 7.61 (d, 1 H), 7.5 (d, 1 H), 7.2  
(d+dd, 2 H), 7.15 (d, 1 H), 6.52 (d, 1 H), 6.15 (d, 1 H), 4.85 (t, 1 H), 4.68 (t, 2 H), 4.35 (s, 2  
H), 4.2 (m, 2 H), 3.95 (q, 2 H), 3.8 (s, 3 H), 3.4 (q, 2 H), 3.18 (m, 2 H), 2.78 (s, 3 H), 2.22 (s, 3  
20 H), 1.9 (m, 2 H), 1.39 (m, 2 H), 1 (t, 3 H)

**STEP 3 : Preparation of ethyl 3-[1-(4-bromobutyl)-4-methyl-1*H*-benzotriazol-5-yl]-3-{3-  
[(6-hydroxy-8-methoxy-2,2-dioxo-2*H*-1,2λ<sup>6</sup>,3-benzoxathiazin-3(4*H*)-  
yl)methyl]-4-methylphenyl}propanoate**

25

Using General Procedure 9 starting from ethyl 3-[1-(4-hydroxybutyl)-4-methyl-1*H*-  
benzotriazol-5-yl]-3-{3-[(6-hydroxy-8-methoxy-2,2-dioxo-2*H*-1,2λ<sup>6</sup>,3-benzoxathiazin-3(4*H*)-  
yl)methyl]-4-methylphenyl}propanoate (1 eq.) as a reactant, the title compound (yellow solid,  
86% yield) was obtained.

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<sup>1</sup>H-NMR (400 MHz, DMSO-d<sub>6</sub>) δ ppm: 9.69 (s, 1 H), 7.62 (d, 1 H), 7.5 (d, 1 H), 7.2 (d, 1 H), 7.19 (dd, 1 H), 7.11 (d, 1 H), 6.5 (d, 1 H), 6.11 (d, 1 H), 4.82 (t, 1 H), 4.68 (t, 2 H), 4.32 (s, 2 H), 4.19 (m, 2 H), 3.91 (q, 2 H), 3.79 (s, 3 H), 3.51 (t, 2 H), 3.18 (m, 2 H), 2.73 (s, 3 H), 2.2 (s, 3 H), 1.99 (m, 2 H), 1.78 (m, 2 H), 1 (t, 3 H)

5

**STEP 4 : Preparation of ethyl [24-methoxy-4,31-dimethyl-27,27-dioxo-21,26-dioxa-27λ<sup>6</sup>-thia-1,14,15,16-tetraazahexacyclo[20.5.3.1<sup>3,7</sup>.1<sup>9,13</sup>.0<sup>12,16</sup>.0<sup>25,29</sup>]dotriaconta-3(32),4,6,9(31),10,12,14,22,24,29-decaen-8-yl]acetate**

10 Using General Procedure 11 starting from ethyl 3-[1-(4-bromobutyl)-4-methyl-1*H*-benzotriazol-5-yl]-3-{3-[(6-hydroxy-8-methoxy-2,2-dioxo-2*H*-1,2λ<sup>6</sup>,3-benzoxathiazin-3(4*H*)-yl)methyl]-4-methylphenyl}propanoate (1 eq.) as a reactant, the title compound (white solid, 73% yield) was obtained.

15 The enantiopure final intermediates were obtained by chromatographic separation on chiral column.

<sup>1</sup>H-NMR (400 MHz, DMSO-d<sub>6</sub>) δ ppm: 7.69 (d, 1 H), 7.48 (dd, 1 H), 7.42 (d, 1 H), 7.29 (d, 1 H), 6.57/6.51 (2d, 2 H), 5.32 (d, 1 H), 4.79 (m, 3 H), 4.12/3.8 (2d, 2 H), 3.91/3.8 (2d, 2 H), 3.91 (q, 2 H), 3.74 (s, 3 H), 3.6/3.39 (m, 2 H), 3.14/3.03 (m, 2 H), 2.61 (s, 3 H), 2.3 (s, 3 H), 2.2/2.05 (m, 2 H), 1.8/1.6 (m, 2 H), 1 (t, 3 H)

20

**STEP 5 : Preparation of EXAMPLE 16**

Using General Procedure 12 starting from ethyl [24-methoxy-4,31-dimethyl-27,27-dioxo-21,26-dioxa-27λ<sup>6</sup>-thia-1,14,15,16-tetraazahexacyclo[20.5.3.1<sup>3,7</sup>.1<sup>9,13</sup>.0<sup>12,16</sup>.0<sup>25,29</sup>]dotriaconta-3(32),4,6,9(31),10,12,14,22,24,29-decaen-8-yl]acetate E1 (1 eq.) or E2 (1 eq.) as reactants, the title compounds (85% - 67% yields respectively) were obtained.

25

#### **Example 16a (E1)**

**HRMS** calculated for C<sub>30</sub>H<sub>32</sub>N<sub>4</sub>O<sub>7</sub>S: 592.1992; [M+H]<sup>+</sup> found: 593.2070 (δ=0.9 ppm)

30

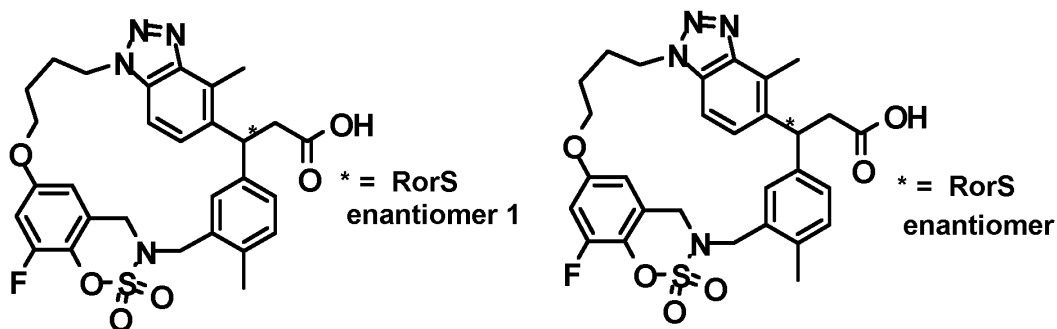
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**Example 16b (E2)**

**HRMS** calculated for  $C_{30}H_{32}N_4O_7S$ : 592.1992;  $[M+H]^+$  found:  $[M+H]^+=593.2073$  ( $\delta=1.4$  ppm)

**$^1H$ -NMR** (400 MHz, DMSO- $d_6$ )  $\delta$  ppm: 12.2 (m, 1 H), 7.68 (d, 1 H), 7.49 (dd, 1 H), 7.41 (d, 1 H), 7.29 (d, 1 H), 5.31 (d, 1 H), 4.75 (m, 3 H), 4.11/3.92 (2d, 2 H), 3.98/3.8 (2d, 2 H), 3.73 (s, 3 H), 3.59/3.33 (2m, 2 H), 3.52/3.51 (2d, 2 H), 3.05/2.92 (2dd, 2 H), 2.6 (s, 3 H), 2.3 (s, 3 H), 2.19/2.07 (2m, 2 H), 1.8/1.6 (2m, 2 H)

**EXAMPLE 17** : [24-Fluoro-4,31-dimethyl-27,27-dioxo-21,26-dioxa-27 $\lambda^6$ -thia-1,14,15,16-tetraazahexacyclo[20.5.3.1<sup>3,7</sup>.1<sup>9,13</sup>.0<sup>12,16</sup>.0<sup>25,29</sup>]dotriaconta-3(32),4,6,9(31),10,12,14,22,24,29-decaen-8-yl]acetic acid



**STEP C1 : Preparation of 6-bromo-8-fluoro-2H-1,2 $\lambda^6$ ,3-benzoxathiazine-2,2-dione**

Using General Procedure 4 STEP 2 starting from 5-bromo-3-fluoro-2-hydroxybenzaldehyde (1 eq.) as a reactant, the title compound (25% yield) was obtained.

**$^1H$ -NMR** (400 MHz, DMSO- $d_6$ )  $\delta$  ppm: 9.2 (s, 1 H), 8.3 (dd, 1 H), 8.1 (s, 1 H)

20

**STEP C2 : Preparation of 6-bromo-8-fluoro-3,4-dihydro-2H-1,2 $\lambda^6$ ,3-benzoxathiazine-2,2-dione**

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Using General Procedure 4 STEP 3 starting from 6-bromo-8-fluoro-2*H*-1,2λ<sup>6</sup>,3-benzoxathiazine-2,2-dione (1 eq.) as a reactant, the title compound (87% yield) was obtained.

<sup>1</sup>H-NMR (400 MHz, DMSO-d<sub>6</sub>) δ ppm: 8.91 (sl, 1 H), 7.72 (dd, 1 H), 7.41 (tf, 1 H), 4.68 (s, 2 H)

5

**STEP C3 : Preparation of *tert*-butyl 6-bromo-8-fluoro-2,2-dioxo-2*H*-1,2λ<sup>6</sup>,3-benzoxathiazine-3(4*H*)-carboxylate**

Using General Procedure 5 STEP 1 starting from 6-bromo-8-fluoro-3,4-dihydro-2*H*-1,2λ<sup>6</sup>,3-benzoxathiazine-2,2-dione (1 eq.) as a reactant, the title compound (85% yield) was obtained.

10

<sup>1</sup>H-NMR (400 MHz, DMSO-d<sub>6</sub>) δ ppm: 7.88 (d, 1 H), 7.74 (s, 1 H), 5.18 (s, 2 H), 1.5 (s, 9 H)

**STEP C4 : Preparation of *tert*-butyl 8-fluoro-2,2-dioxo-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2*H*-1,2λ<sup>6</sup>,3-benzoxathiazine-3(4*H*)-carboxylate**

15

Using General Procedure 5 STEP 2 starting from *tert*-butyl 6-bromo-8-fluoro-2,2-dioxo-2*H*-1,2λ<sup>6</sup>,3-benzoxathiazine-3(4*H*)-carboxylate (1 eq.) as a reactant, the title compound (71% yield) was obtained.

<sup>1</sup>H-NMR (400 MHz, DMSO-d<sub>6</sub>) δ ppm: 7.69 (s, 1 H), 7.57 (d, 1 H), 5.21 (s, 2 H), 1.49 (s, 9 H),

20

1.31 (s, 12 H)

**STEP C5 : Preparation of *tert*-butyl 8-fluoro-6-hydroxy-2,2-dioxo-2*H*-1,2λ<sup>6</sup>,3-benzoxathiazine-3(4*H*)-carboxylate**

Using General Procedure 5 STEP 3 starting from *tert*-butyl 8-fluoro-2,2-dioxo-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2*H*-1,2λ<sup>6</sup>,3-benzoxathiazine-3(4*H*)-carboxylate (1 eq.) as a reactant, the title compound (81% yield) was obtained.

<sup>1</sup>H-NMR (400 MHz, DMSO-d<sub>6</sub>) δ ppm: 10.4 (m, 1 H), 6.79 (dd, 1 H), 6.78 (d, 1 H), 5.02 (s, 2 H), 1.49 (s, 9 H)

30

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**STEP C6 : Preparation of 6-(benzyloxy)-8-fluoro-3,4-dihydro-2H-1,2λ<sup>6</sup>,3-benzoxathiazine-2,2-dione**

Using General Procedure 5 STEP 4 starting from *tert*-butyl 8-fluoro-6-hydroxy-2,2-dioxo-2H-1,2λ<sup>6</sup>,3-benzoxathiazine-3(4H)-carboxylate (1 eq.) as a reactant, *tert*-butyl 6-(benzyloxy)-8-fluoro-2,2-dioxo-2H-1,2λ<sup>6</sup>,3-benzoxathiazine-3(4H)-carboxylate (36% yield) was obtained. The crude product was reacted using General Procedure 5 STEP 5 resulting the title compound (91% yield).

<sup>1</sup>H-NMR (400 MHz, DMSO-d<sub>6</sub>) δ ppm: 8.7 (m, 1 H), 7.48-7.3 (m, 5 H), 7.1 (dd, 1 H), 6.8 (d, 1 H), 5.09 (s, 2 H), 4.58 (s, 2 H)

**STEP 1 : Preparation of ethyl 3-(3-{[6-(benzyloxy)-8-fluoro-2,2-dioxo-2H-1,2λ<sup>6</sup>,3-benzoxathiazin-3(4H)-yl]methyl}-4-methylphenyl)-3-(1-{4-[(4-methoxyphenyl)methoxy]butyl}-4-methyl-1H-benzotriazol-5-yl)propanoate**

Using General Procedure 7 starting from ethyl 3-[3-(hydroxymethyl)-4-methylphenyl]-3-(1-{4-[(4-methoxyphenyl)methoxy]butyl}-4-methyl-1H-benzotriazol-5-yl)propanoate (1 eq.) and 6-(benzyloxy)-8-fluoro-3,4-dihydro-2H-1,2λ<sup>6</sup>,3-benzoxathiazine-2,2-dione (1 eq.) as reactants, the title compound (85% yield) was obtained.

<sup>1</sup>H-NMR (400 MHz, DMSO-d<sub>6</sub>) δ ppm: 0.97 (t, J=7.09 Hz, 3 H) 1.39 - 1.51 (m, 2 H) 1.89 (quint, J=7.27 Hz, 2 H) 1.99 (s, 2 H) 2.22 (s, 3 H) 2.76 (s, 3 H) 3.16 (dd, J=8.07, 2.69 Hz, 2 H) 3.35 (t, J=6.30 Hz, 2 H) 3.72 (s, 3 H) 3.92 (q, J=7.05 Hz, 2 H) 4.24 - 4.32 (m, 4 H) 4.49 (s, 2 H) 4.60 (t, J=6.97 Hz, 2 H) 4.84 (t, J=8.07 Hz, 1 H) 5.11 (s, 2 H) 6.79 (s, 1 H) 6.82 - 6.89 (m, 2 H) 7.10 - 7.22 (m, 5 H) 7.24 (s, 1 H) 7.32 - 7.50 (m, 6 H) 7.53 - 7.59 (m, 1 H)

**STEP 2 : Preparation of ethyl 3-{3-[(8-fluoro-6-hydroxy-2,2-dioxo-2H-1,2λ<sup>6</sup>,3-benzoxathiazin-3(4H)-yl)methyl]-4-methylphenyl}-3-[1-(4-hydroxybutyl)-4-methyl-1H-benzotriazol-5-yl]propanoate**

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Using General Procedure 8 starting from ethyl 3-(3-{[6-(benzyloxy)-8-fluoro-2,2-dioxo-2*H*-1,2λ<sup>6</sup>,3-benzoxathiazin-3(4*H*)-yl]methyl}-4-methylphenyl)-3-(1-{4-[(4-methoxyphenyl)methoxy]butyl}-4-methyl-1*H*-benzotriazol-5-yl)propanoate (1 eq.) as a reactant, the title compound (white solid, 97% yield) was obtained.

5 <sup>1</sup>H-NMR (400 MHz, DMSO-d<sub>6</sub>) δ ppm: 10.1/4.4 (s+t, 2 H), 7.62 (d, 1 H), 7.5 (d, 1 H), 7.28 (d, 1 H), 7.2 (dd, 1 H), 7.15 (d, 1 H), 6.78 (dd, 1 H), 6.48 (d, 1 H), 4.85 (t, 1 H), 4.65 (t, 2 H), 4.49 (s, 2 H), 4.28 (m, 2 H), 3.95 (q, 2 H), 3.4 (q, 2 H), 3.18 (d, 2 H), 2.78 (s, 3 H), 2.22 (s, 3 H), 1.9 (m, 2 H), 1.38 (m, 2 H), 1 (t, 3 H)

10 **STEP 3 : Preparation of ethyl 3-[1-(4-bromobutyl)-4-methyl-1*H*-benzotriazol-5-yl]-3-{[(8-fluoro-6-hydroxy-2,2-dioxo-2*H*-1,2λ<sup>6</sup>,3-benzoxathiazin-3(4*H*)-yl)methyl]-4-methylphenyl}propanoate**

Using General Procedure 9 starting from ethyl 3-{3-[(8-fluoro-6-hydroxy-2,2-dioxo-2*H*-1,2λ<sup>6</sup>,3-benzoxathiazin-3(4*H*)-yl)methyl]-4-methylphenyl}-3-[1-(4-hydroxybutyl)-4-methyl-1*H*-benzotriazol-5-yl]propanoate (1 eq.) as a reactant, the title compound (off-white solid, 65% yield) was obtained.

15 <sup>1</sup>H-NMR (400 MHz, DMSO-d<sub>6</sub>) δ ppm: 10.1 (s, 1 H), 7.62 (d, 1 H), 7.5 (d, 1 H), 7.22 (d, 1 H), 7.19 (dd, 1 H), 7.12 (d, 1 H), 6.78 (d, 1 H), 6.45 (d, 1 H), 4.83 (t, 1 H), 4.69 (t, 2 H), 4.48 (s, 2 H), 4.26 (m, 2 H), 3.91 (q, 2 H), 3.51 (t, 2 H), 3.15 (m, 2 H), 2.73 (s, 3 H), 2.21 (s, 3 H), 2 (m, 2 H), 1.78 (m, 2 H), 1 (t, 3 H)

25 **STEP 4 : Preparation of ethyl [24-fluoro-4,31-dimethyl-27,27-dioxo-21,26-dioxa-27λ<sup>6</sup>-thia-1,14,15,16-tetraazahexacyclo[20.5.3.1<sup>3,7</sup>.1<sup>9,13</sup>.0<sup>12,16</sup>.0<sup>25,29</sup>]dotriacont-3(32),4,6,9(31),10,12,14,22,24,29-decaen-8-yl]acetate**

Using General Procedure 11 starting from ethyl 3-[1-(4-bromobutyl)-4-methyl-1*H*-benzotriazol-5-yl]-3-{3-[(8-fluoro-6-hydroxy-2,2-dioxo-2*H*-1,2λ<sup>6</sup>,3-benzoxathiazin-3(4*H*)-yl)methyl]-4-methylphenyl}propanoate (1 eq.) as a reactant, the title compound (off-white solid, 74% yield) was obtained.

30



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The enantiopure final intermediates were obtained by chromatographic separation on chiral column.

**<sup>1</sup>H-NMR** (400 MHz, DMSO-d<sub>6</sub>) δ ppm: 7.68 (d, 1 H), 7.49 (dd, 1 H), 7.41 (d, 1 H), 7.3 (d, 1 H), 6.9 (dd, 1 H), 6.6 (d, 1 H), 5.75 (d, 1 H), 4.79 (m, 3 H), 4.2/4.02 (2d, 2 H), 4.02/3.95 (2d, 2 H), 3.95 (q, 2 H), 3.7/3.5 (2m, 2 H), 3.18/3.05 (2dd, 2 H), 2.63 (s, 3 H), 2.32 (s, 3 H), 2.2/2.05 (2m, 2 H), 1.8/1.62 (2m, 2 H), 1 (t, 3 H)

#### STEP 5 : Preparation of EXAMPLE 17

Using General Procedure 12 starting from ethyl [24-fluoro-4,31-dimethyl-27,27-dioxo-21,26-dioxa-27λ<sup>6</sup>-thia-1,14,15,16-tetraazahexacyclo[20.5.3.1<sup>3,7</sup>.1<sup>9,13</sup>.0<sup>12,16</sup>.0<sup>25,29</sup>]dotriaconta-3(32),4,6,9(31),10,12,14,22,24,29-decaen-8-yl]acetate E1 (1 eq.) or E2 (1 eq.) as reactants, the title compounds (65% - 99% yields respectively) were obtained.

#### 15 **Example 17a (E1)**

**HRMS** calculated for C<sub>29</sub>H<sub>29</sub>FN<sub>4</sub>O<sub>6</sub>S: 580.1792; [M+H]<sup>+</sup> found: 581.1871 (δ=1.1 ppm)

#### **Example 17b (E2)**

**HRMS** calculated for C<sub>29</sub>H<sub>29</sub>FN<sub>4</sub>O<sub>6</sub>S: 580.1792; [M+H]<sup>+</sup> found: 581.1867 (δ=0.4 ppm)

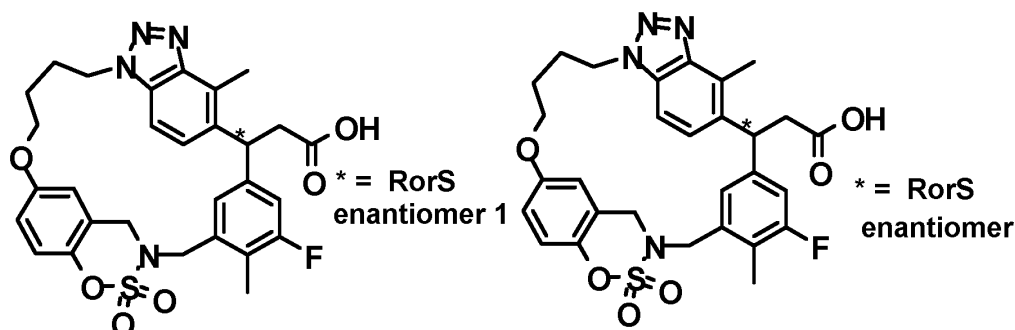
**<sup>1</sup>H-NMR** (400 MHz, DMSO-d<sub>6</sub>) δ ppm: 12.3 (m, 1 H), 7.55 (d, 1 H), 7.5 (dd, 1 H), 7.4 (d, 1 H), 7.3 (d, 1 H), 6.9 (dd, 1 H), 6.55 (d, 1 H), 5.7 (sl, 1 H), 4.8 (m, 3 H), 4.15/4 (2d, 2 H), 4/3.9 (2d, 2 H), 3.7/3.5 (2m, 2 H), 3/2.9 (2m, 2 H), 2.6 (s, 3 H), 2.3 (s, 3 H), 2.2/2.1 (2m, 2 H), 1.8/1.6 (2m, 2 H)

**<sup>19</sup>F-NMR** (376 MHz, DMSO-d<sub>6</sub>) δ ppm: 133

25

**EXAMPLE 18 : [5-Fluoro-4,31-dimethyl-27,27-dioxo-21,26-dioxa-27λ<sup>6</sup>-thia-1,14,15,16-tetraazahexacyclo[20.5.3.1<sup>3,7</sup>.1<sup>9,13</sup>.0<sup>12,16</sup>.0<sup>25,29</sup>]dotriaconta-3(32),4,6,9(31),10,12,14,22,24,29-decaen-8-yl]acetic acid**

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### STEP B1 : Preparation of (5-bromo-3-fluoro-2-methylphenyl)methanol

5 Lithium aluminium hydride (4 eq., 3.07 g, 80.9 mmol) was placed into a round bottom flask. After addition of abs. THF (5 mL/mmol, 101 ml), the mixture was cooled to 0 °C. A solution of methyl 5-bromo-3-fluoro-2-methylbenzoate (5 g, 20.2 mmol) in abs. THF (5 mL/mmol, 101 mL) was added dropwise at 0°C while continuous stirring. The reaction mixture was allowed to warm to RT and was stirred at this temperature overnight. After completion of the reaction the

10 mixture was quenched carefully with 150 mL of water and 100 mL 2M aq. NaOH solution was added. The mixture was concentrated to dryness, then it was purified by normal phase silica gel chromatography using DCM-EtOH (90:10) as an eluent to give the title compound (1.8 g, 41% yield).

<sup>1</sup>H-NMR (400 MHz, DMSO-d<sub>6</sub>) δ ppm: 7.41 (d, 1 H), 7.35 (dd, 1 H), 5.35 (t, 1 H), 4.5 (d, 2 H), 2.1 (s, 3 H)

15

### STEP B2 : Preparation of [3-fluoro-2-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]methanol

20 Using General Procedure 3 starting from (5-bromo-3-fluoro-2-methylphenyl)methanol (1 eq., 1.8 g, 8.2 mmol) as a reactant, the title compound (2.5 g, 73% yield) was obtained.

<sup>1</sup>H-NMR (400 MHz, DMSO-d<sub>6</sub>) δ ppm: 7.55 (s, 1 H), 7.2 (d, 1 H), 5.2 (t, 1 H), 4.52 (d, 2 H), 2.18 (s, 3 H), 1.31 (s, 12 H)

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**STEP 1 : Preparation of ethyl 3-[3-fluoro-5-(hydroxymethyl)-4-methylphenyl]-3-(1-{4-[(4-methoxyphenyl)methoxy]butyl}-4-methyl-1*H*-benzotriazol-5-yl)propanoate**

5 Using General Procedure 6 starting from ethyl (2*E*)-3-(1-{4-[(4-methoxyphenyl)methoxy]butyl}-4-methyl-1*H*-benzotriazol-5-yl)prop-2-enoate (1 eq.) and [3-fluoro-2-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]methanol (1.4 eq.) as reactants, the title compound (32% yield) was obtained.

<sup>1</sup>H-NMR (400 MHz, DMSO-d<sub>6</sub>) δ ppm: 7.6 (d, 1 H), 7.5 (d, 1 H), 7.2 (d, 2 H), 7.12 (sl, 1 H),  
10 7.05 (d, 1 H), 6.9 (d, 2 H), 5.1 (t, 1 H), 4.82 (t, 1 H), 4.65 (t, 2 H), 4.45 (d, 2 H), 4.32 (s, 2 H),  
3.95 (q, 2 H), 3.72 (s, 3 H), 3.4 (t, 2 H), 3.15 (t, 2 H), 2.78 (s, 3 H), 2.08 (s, 3 H), 1.92 (m, 2  
H), 1.5 (m, 2 H), 1 (t, 3 H)

**STEP 2 : Preparation of ethyl 3-(3-{[6-(benzyloxy)-2,2-dioxo-2*H*-1,2λ<sup>6</sup>,3-benzoxathiazin-3(4*H*)-yl]methyl}-5-fluoro-4-methylphenyl)-3-(1-{4-[(4-methoxyphenyl)methoxy]butyl}-4-methyl-1*H*-benzotriazol-5-yl)propanoate**

Using General Procedure 7 starting from ethyl 3-[3-fluoro-5-(hydroxymethyl)-4-methylphenyl]-3-(1-{4-[(4-methoxyphenyl)methoxy]butyl}-4-methyl-1*H*-benzotriazol-5-yl)propanoate (1 eq.) and 6-(benzyloxy)-3,4-dihydro-2*H*-1,2λ<sup>6</sup>,3-benzoxathiazine-2,2-dione (1.1 eq.) as reactants, the title compound (91% yield) was obtained.

<sup>1</sup>H-NMR (400 MHz, DMSO-d<sub>6</sub>) δ ppm: 7.6/7.5 (2d, 2 H), 7.45 (dl, 2 H), 7.4 (t, 2 H), 7.35 (tl, 1 H), 7.2 (d, 2 H), 7.1 (m, 3 H), 7.05 (dd, 1 H), 6.95 (d, 1 H), 6.85 (d, 2 H), 5.1 (s, 2 H), 4.85 (t, 1 H), 4.6 (t, 2 H), 4.45-4.25 (3s, 6 H), 3.95 (q, 2 H), 3.7 (s, 3 H), 3.35 (t, 2 H), 3.2 (m, 2 H),  
25 2.8 (sl, 3 H), 2.1 (sl, 3 H), 1.9 (quint, 2 H), 1.45 (quint, 2 H), 1 (t, 3 H)

**STEP 3 : Preparation of ethyl 3-{3-fluoro-5-[(6-hydroxy-2,2-dioxo-2*H*-1,2λ<sup>6</sup>,3-benzoxathiazin-3(4*H*)-yl)methyl]-4-methylphenyl}-3-[1-(4-hydroxybutyl)-4-methyl-1*H*-benzotriazol-5-yl]propanoate**

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Using General Procedure 8 starting from ethyl 3-(3-{[6-(benzyloxy)-2,2-dioxo-2*H*-1,2λ<sup>6</sup>,3-benzoxathiazin-3(4*H*)-yl]methyl}-5-fluoro-4-methylphenyl)-3-(1-{4-[(4-methoxyphenyl)methoxy]butyl}-4-methyl-1*H*-benzotriazol-5-yl)propanoate (1 eq.) as a reactant, the title compound (white solid, quant.) was obtained.

- 5 <sup>1</sup>H-NMR (400 MHz, DMSO-d<sub>6</sub>) δ ppm: 9.7 (s, 1 H), 7.6 (d, 1 H), 7.5 (d, 1 H), 7.15 (m, 2 H), 7 (d, 1 H), 6.8 (dd, 1 H), 6.6 (d, 1 H), 4.85 (t, 1 H), 4.65 (t, 2 H), 4.4 (m, 3 H), 4.25 (2d, 2 H), 3.9 (q, 2 H), 3.4 (q, 2 H), 3.2 (m, 2 H), 2.8 (s, 3 H), 2.1 (d, 3 H), 1.9 (quint, 2 H), 1.4 (quint, 2 H), 1 (t, 3 H)

10 **STEP 4 : Preparation of ethyl 3-[1-(4-bromobutyl)-4-methyl-1*H*-benzotriazol-5-yl]-3-{3-fluoro-5-[(6-hydroxy-2,2-dioxo-2*H*-1,2λ<sup>6</sup>,3-benzoxathiazin-3(4*H*)-yl)methyl]-4-methylphenyl}propanoate**

- Using General Procedure 9 starting from ethyl 3-{3-fluoro-5-[(6-hydroxy-2,2-dioxo-2*H*-1,2λ<sup>6</sup>,3-benzoxathiazin-3(4*H*)-yl)methyl]-4-methylphenyl}-3-[1-(4-hydroxybutyl)-4-methyl-1*H*-benzotriazol-5-yl]propanoate (1 eq.) as a reactant, the title compound (white solid, 73% yield) was obtained.

- <sup>1</sup>H-NMR (400 MHz, DMSO-d<sub>6</sub>) δ ppm: 9.7 (s, 1 H), 7.65/7.5 (2d, 2 H), 7.15 (m, 2 H), 7 (d, 1 H), 6.8 (dd, 1 H), 6.6 (d, 1 H), 4.85 (t, 1 H), 4.7 (t, 2 H), 4.4 (2d, 2 H), 4.25 (2d, 2 H), 3.9 (q, 2 H), 3.5 (t, 2 H), 3.2 (m, 2 H), 2.75 (sl, 3 H), 2.1 (d, 3 H), 2 (m, 2 H), 1.8 (quint, 2 H), 1 (t, 3 H)

**STEP 5 : Preparation of ethyl [5-fluoro-4,31-dimethyl-27,27-dioxo-21,26-dioxa-27λ<sup>6</sup>-thia-1,14,15,16-tetraazahexacyclo[20.5.3.1<sup>3,7</sup>.1<sup>9,13</sup>.0<sup>12,16</sup>.0<sup>25,29</sup>]dotriacont-3(32),4,6,9(31),10,12,14,22,24,29-decaen-8-yl]acetate**

25

Using General Procedure 11 starting from ethyl 3-[1-(4-bromobutyl)-4-methyl-1*H*-benzotriazol-5-yl]-3-{3-fluoro-5-[(6-hydroxy-2,2-dioxo-2*H*-1,2λ<sup>6</sup>,3-benzoxathiazin-3(4*H*)-yl)methyl]-4-methylphenyl}propanoate (1 eq.) as a reactant, the title compound (96% yield) was obtained.

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The enantiopure final intermediates were obtained by chromatographic separation on chiral column.

**<sup>1</sup>H-NMR** (400 MHz, DMSO-d<sub>6</sub>) δ ppm: 1.17 (t, J=7.15 Hz, 3 H) 1.58 (dt, J=13.63, 6.76 Hz, 1 H) 1.70 - 1.86 (m, 1 H) 2.20 - 2.27 (m, 3 H) 2.65 (s, 3 H) 3.05 (dd, J=15.83, 8.74 Hz, 1 H) 3.16  
5 - 3.26 (m, 1 H) 3.43 - 3.57 (m, 1 H) 3.62 - 3.73 (m, 1 H) 3.83 - 4.00 (m, 7 H) 4.03 - 4.17 (m, 4 H) 4.63 - 4.89 (m, 4 H) 5.89 (d, J=2.81 Hz, 1 H) 6.45 (s, 1 H) 6.79 (dd, J=9.05, 2.93 Hz, 1 H) 6.97 - 7.01 (m, 1 H) 7.39 - 7.47 (m, 2 H) 7.68 (d, J=8.68 Hz, 1 H)

#### STEP 6 : Preparation of EXAMPLE 18

10

Using General Procedure 12 starting from ethyl [5-fluoro-4,31-dimethyl-27,27-dioxo-21,26-dioxa-27λ<sup>6</sup>-thia-1,14,15,16-tetraazahexacyclo[20.5.3.1<sup>3,7</sup>.1<sup>9,13</sup>.0<sup>12,16</sup>.0<sup>25,29</sup>]dotriaconta-3(32),4,6,9(31),10,12,14,22,24,29-decaen-8-yl]acetate E1 (1 eq.) or E2 (1 eq.) as reactants the title compounds (80% - 72% yields respectively) were obtained.

15

##### Example 18a (E1)

**HRMS** calculated for C<sub>29</sub>H<sub>29</sub>FN<sub>4</sub>O<sub>6</sub>S: 580.1792; [M+H]<sup>+</sup> found: 581.1867 (δ=0.4 ppm)

##### Example 18b (E2)

20

**HRMS** calculated for C<sub>29</sub>H<sub>29</sub>FN<sub>4</sub>O<sub>6</sub>S: 580.1792; [M+H]<sup>+</sup> found: 581.1866 (δ=0.2 ppm)

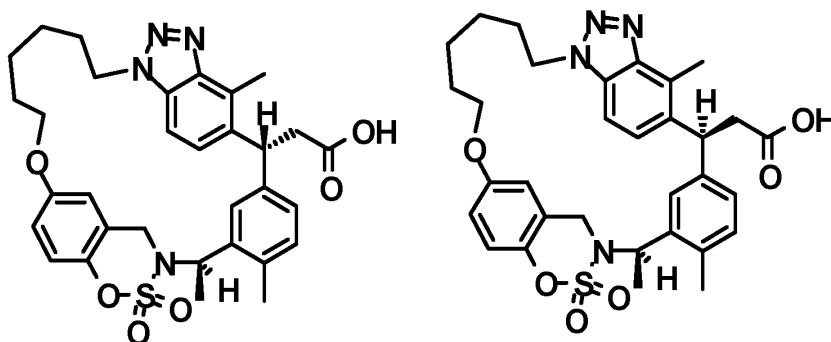
**<sup>1</sup>H-NMR** (400 MHz, DMSO-d<sub>6</sub>) δ ppm: 12.2 (m, 1 H), 7.7 (d, 1 H), 7.41 (2d, 2 H), 7 (d, 1 H), 6.8 (dd, 1 H), 6.45 (d, 1 H), 5.9 (d, 1 H), 4.79 (m, 3 H), 4.09 (m, 2 H), 3.91 (m, 2 H), 3.68/3.45 (2m, 2 H), 3.1/2.95 (2dd, 2 H), 2.65 (s, 3 H), 2.22 (s, 3 H), 2.2/2.05 (2m, 2 H), 1.8/1.6 (2m, 2 H)  
H)

25

**EXAMPLE 19** : [(2*R*,8*R*)-2,4,33-Trimethyl-29,29-dioxo-23,28-dioxa-29λ<sup>6</sup>-thia-1,14,15,16-tetraazahexacyclo[22.5.3.1<sup>3,7</sup>.1<sup>9,13</sup>.0<sup>12,16</sup>.0<sup>27,31</sup>]tetratriaconta-3(34),4,6,9(33),10,12,14,24,26,31-decaen-8-yl]acetic acid and

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[(2*R*,8*S*)-2,4,33-trimethyl-29,29-dioxo-23,28-dioxa-29 $\lambda^6$ -thia-1,14,15,16-tetraazahexacyclo[22.5.3.1<sup>3,7</sup>.1<sup>9,13</sup>.0<sup>12,16</sup>.0<sup>27,31</sup>]tetratriaconta-3(34),4,6,9(33),10,12,14,24,26,31-decaen-8-yl]acetic acid



5

**STEP 1 : Preparation of ethyl 3-{1-[6-(benzyloxy)hexyl]-4-methyl-1*H*-benzotriazol-5-yl}-3-{3-[(1*S*)-1-hydroxyethyl]-4-methylphenyl}propanoate**

10 Using General Procedure 6 starting from ethyl (2*E*)-3-{1-[6-(benzyloxy)hexyl]-4-methyl-1*H*-benzotriazol-5-yl}prop-2-enoate (1 eq.) (1*S*)-1-[2-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]ethan-1-ol (2 eq.) as reactants, the title compound (70% yield) was obtained.

15 **<sup>1</sup>H-NMR** (400 MHz, DMSO-*d*<sub>6</sub>)  $\delta$  ppm: 7.59 (d, 1 H), 7.46 (d, 1 H), 7.4 (d, 1 H), 7.34-7.22 (br, 5 H), 6.99 (d, 1 H), 4.97 (d, 1 H), 4.82 (m, 1 H), 4.82 (m, 1 H), 4.62 (dd, 2 H), 4.4 (s, 2 H), 4.05 (dd, 1 H), 3.92 (q, 2 H), 3.36 (t, 2 H), 3.11 (m, 2 H), 2.75 (s, 3 H), 2.19 (s, 3 H), 1.87 (quint, 2 H), 1.48 (quint, 2 H), 1.32 (quint, 2 H), 1.22 (m, 3 H), 1.22 (m, 2 H), 0.99 (t, 3 H)

20 **STEP 2 : Preparation of ethyl 3-(3-{(1*R*)-1-[6-(benzyloxy)-2,2-dioxo-2*H*-1,2 $\lambda^6$ ,3-benzoxathiazin-3(4*H*)-yl]ethyl}-4-methylphenyl)-3-{1-[6-(benzyloxy)hexyl]-4-methyl-1*H*-benzotriazol-5-yl}propanoate**

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Using General Procedure 7 starting from ethyl 3-{1-[6-(benzyloxy)hexyl]-4-methyl-1*H*-benzotriazol-5-yl}-3-{3-[(1*S*)-1-hydroxyethyl]-4-methylphenyl}propanoate (1 eq.) and 6-(benzyloxy)-3,4-dihydro-2*H*-1,2λ<sup>6</sup>,3-benzoxathiazine-2,2-dione (1.5 eq.) as reactants, the title compound (beige solid, 71% yield) was obtained.

- 5 <sup>1</sup>H-NMR (400 MHz, DMSO-d<sub>6</sub>) δ ppm: 0.95 - 1.00 (m, 3 H) 1.23 - 1.36 (m, 3 H) 1.37 - 1.49 (m, 5 H) 1.83 (sxt, J=6.85 Hz, 2 H) 1.99 (s, 1 H) 2.28 (s, 3 H) 2.76 (d, J=3.67 Hz, 3 H) 3.14 - 3.26 (m, 2 H) 3.33 - 3.36 (m, 1 H) 3.86 - 3.97 (m, 2 H) 4.27 - 4.49 (m, 4 H) 4.59 (q, J=6.64 Hz, 2 H) 4.87 (td, J=7.98, 4.10 Hz, 1 H) 5.02 - 5.14 (m, 2 H) 5.27 (q, J=6.93 Hz, 1 H) 6.96 - 7.16 (m, 4 H) 7.24 - 7.48 (m, 11 H) 7.49 - 7.55 (m, 1 H) 7.57 - 7.63 (m, 1 H)

10

**STEP 3 : Preparation of ethyl 3-{3-[(1*R*)-1-(6-hydroxy-2,2-dioxo-2*H*-1,2λ<sup>6</sup>,3-benzoxathiazin-3(4*H*)-yl)ethyl]-4-methylphenyl}-3-[1-(6-hydroxyhexyl)-4-methyl-1*H*-benzotriazol-5-yl]propanoate**

- 15 Using General Procedure 8 starting from ethyl 3-(3-{(1*R*)-1-[6-(benzyloxy)-2,2-dioxo-2*H*-1,2λ<sup>6</sup>,3-benzoxathiazin-3(4*H*)-yl]ethyl}-4-methylphenyl)-3-[1-[6-(benzyloxy)hexyl]-4-methyl-1*H*-benzotriazol-5-yl]propanoate (1 eq.) as a reactant, the title compound (grey solid, 78% yield) was obtained.

- 20 <sup>1</sup>H-NMR (400 MHz, DMSO-d<sub>6</sub>) δ ppm: 9.66 (m, 1 H), 7.63/7.56 (2dd, 2 H), 7.47/7.44 (2d, 1 H), 7.15-7.08 (m, 2 H), 6.92/6.9 (2d, 1 H), 6.72 (2dd, 1 H), 6.58 (2dd, 1 H), 5.26 (m, 1 H), 4.87 (m, 1 H), 4.63 (t, 2 H), 4.31 (m, 2 H), 3.94 (2d, 2 H), 3.32 (m, 2 H), 3.22 (d, 2 H), 2.76 (s, 3 H), 2.28 (s, 3 H), 1.87 (m, 2 H), 1.43/1.41 (2d, 3 H), 1.38-1.1 (m, 4 H), 1.33 (m, 2 H), 1/0.99 (2t, 3 H)

- 25 **STEP 4 : Preparation of ethyl 3-[1-(6-bromohexyl)-4-methyl-1*H*-benzotriazol-5-yl]-3-{3-[(1*R*)-1-(6-hydroxy-2,2-dioxo-2*H*-1,2λ<sup>6</sup>,3-benzoxathiazin-3(4*H*)-yl)ethyl]-4-methylphenyl}propanoate**

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Using General Procedure 9 starting from ethyl 3-{3-[(1*R*)-1-(6-hydroxy-2,2-dioxo-2*H*-1,2λ<sup>6</sup>,3-benzoxathiazin-3(4*H*)-yl)ethyl]-4-methylphenyl}-3-[1-(6-hydroxyhexyl)-4-methyl-1*H*-

benzotriazol-5-yl]propanoate (1 eq.) as a reactant, the title compound (84% yield) was obtained.  
<sup>1</sup>H-NMR (400 MHz, DMSO-d<sub>6</sub>) δ ppm: 9.61/9.6 (2s, 1 H), 7.62 (dd, 1 H), 7.58 (d, 1 H),  
 5 7.48/7.42 (2d, 1 H), 7.1 (m, 2 H), 6.91 (d, 1 H), 6.71 (m, 1 H), 6.6/6.53 (2d, 1 H), 5.26 (m, 1 H),  
 4.89 (m, 1 H), 4.62 (t, 2 H), 4.4-4.2 (m, 2 H), 3.92 (2d, 2 H), 3.46 (m, 2 H), 3.21 (d, 2 H), 2.77  
 (s, 3 H), 2.28 (s, 3 H), 1.88 (m, 2 H), 1.71 (m, 2 H), 1.4 (2d, 3 H), 1.38 (m, 2 H), 1.21 (m, 3 H),  
 1 (2t, 1 H)

10 **STEP 5 : Preparation of ethyl [(2*R*)-2,4,33-trimethyl-29,29-dioxo-23,28-dioxa-29λ<sup>6</sup>-thia-  
 1,14,15,16-tetraazahexacyclo[22.5.3.1<sup>3,7</sup>.1<sup>9,13</sup>.0<sup>12,16</sup>.0<sup>27,31</sup>]tetratriaconta-  
 3(34),4,6,9(33),10,12,14,24,26,31-decaen-8-yl]acetate**

Using General Procedure 11 starting from ethyl 3-[1-(6-bromohexyl)-4-methyl-1*H*-  
 15 benzotriazol-5-yl]-3-{3-[(1*R*)-1-(6-hydroxy-2,2-dioxo-2*H*-1,2λ<sup>6</sup>,3-benzoxathiazin-3(4*H*)-  
 yl)ethyl]-4-methylphenyl}propanoate (1 eq.) as a reactant, the title compound (81% yield) was  
 obtained.

<sup>1</sup>H-NMR (400 MHz, DMSO-d<sub>6</sub>) δ ppm: 1.00 (dt, J=11.62, 7.09 Hz, 12 H) 1.20 - 1.29 (m, 9 H)  
 1.29 - 1.76 (m, 25 H) 1.86 - 1.98 (m, 5 H) 2.30 (d, J=9.05 Hz, 10 H) 2.63 - 2.79 (m, 1 H) 2.97  
 20 (dd, J=15.77, 7.46 Hz, 1 H) 3.09 - 3.27 (m, 2 H) 3.64 - 3.76 (m, 1 H) 3.77 - 3.99 (m, 6 H) 4.00  
 - 4.10 (m, 1 H) 4.18 (d, J=17.48 Hz, 1 H) 4.59 - 4.72 (m, 3 H) 4.86 (t, J=8.01 Hz, 1 H) 4.94 (t,  
 J=7.95 Hz, 1 H) 5.24 - 5.42 (m, 3 H) 5.99 (d, J=2.81 Hz, 1 H) 6.40 (d, J=2.81 Hz, 1 H) 6.75 -  
 6.86 (m, 2 H) 6.93 - 7.04 (m, 3 H) 7.09 - 7.20 (m, 2 H) 7.29 (dd, J=12.41, 7.76 Hz, 2 H) 7.47  
 (d, J=7.58 Hz, 1 H) 7.55 (s, 1 H) 7.61 (d, J=8.80 Hz, 1 H) 7.66 (d, J=8.68 Hz, 1 H) 7.77 (d,  
 25 J=8.93 Hz, 1 H)

**STEP 6 : Preparation of EXAMPLE 19**

Using General Procedure 12 starting from ethyl [(2*R*)-2,4,33-trimethyl-29,29-dioxo-23,28-  
 30 dioxa-29λ<sup>6</sup>-thia-1,14,15,16-tetraazahexacyclo[22.5.3.1<sup>3,7</sup>.1<sup>9,13</sup>.0<sup>12,16</sup>.0<sup>27,31</sup>]tetratriaconta-



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3(34),4,6,9(33),10,12,14,24,26,31-decaen-8-yl]acetate (1 eq.) as a reactant, the title compound (white solid, 91% yield) was obtained.

The diastereo-pure products were obtained by chromatographic separation on chiral column.

#### 5 **Example 19a (2R,8R)**

**HRMS** calculated for  $C_{32}H_{36}N_4O_6S$ : 604.2356;  $[M+H]^+$  found: 605.2430 ( $\delta=0.3$  ppm)

**$^1H$ -NMR** (400 MHz, DMSO- $d_6$ )  $\delta$  ppm: 12.2 (sl), 7.6 (d, 1 H), 7.48 (dd, 1 H), 7.3 (d, 1 H), 7.14 (d, 1 H), 7 (d, 1 H), 6.96 (d, 1 H), 6.78 (dd, 1 H), 6 (d, 1 H), 5.3 (q, 1 H), 4.92 (t, 1 H), 4.64 (m, 2 H), 4.04/3.83 (2d, 2 H), 3.7 (m, 2 H), 3.11/2.85 (2dd, 2 H), 2.82 (s, 3 H), 2.32 (s, 3 H), 2 (m, 2 H), 1.6 (m, 2 H), 1.4 (m, 2 H), 1.25 (m, 2 H), 1.25 (d, 3 H)

**$^{13}C$ -NMR** (100 MHz, DMSO- $d_6$ )  $\delta$  ppm: 131.6, 128.4, 128, 126.5, 119.5, 115.7, 111.4, 107.8, 68.4, 55.3, 47.8, 45, 41.6, 39.9, 29.5, 27.5, 25.7, 25.5, 18.7, 15.1, 13.6

#### **Example 19b (2R,8S)**

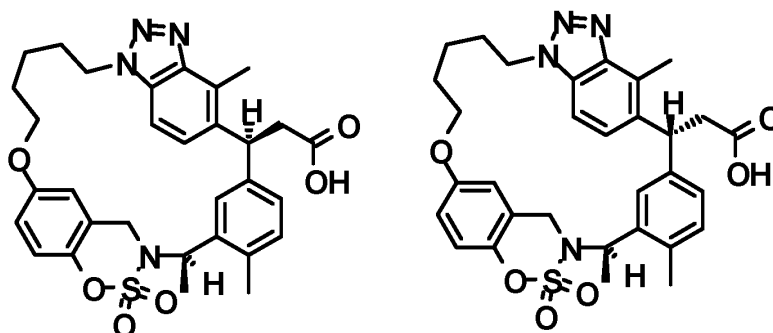
15 **HRMS** calculated for  $C_{32}H_{36}N_4O_6S$ : 604.2356;  $[M+H]^+$  found: 605.2431 ( $\delta=0.4$  ppm)

**$^1H$ -NMR** (400 MHz, DMSO- $d_6$ )  $\delta$  ppm: 12.1 (sl), 7.75 (d, 1 H), 7.65 (d, 1 H), 7.52 (d, 1 H), 7.3 (dd, 1 H), 7.12 (d, 1 H), 7 (d, 1 H), 6.82 (dd, 1 H), 6.4 (d, 1 H), 5.34 (q, 1 H), 4.84 (t, 1 H), 4.67 (m, 2 H), 4.18/3.92 (2d, 2 H), 3.82 (t, 2 H), 3.15/3.05 (2dd, 2 H), 2.82 (s, 3 H), 2.3 (s, 3 H), 1.85 (m, 2 H), 1.7 (m, 2 H), 1.6-1.4 (m, 2 H), 1.5 (d, 3 H), 1.35 (m, 2 H)

20  **$^{13}C$ -NMR** (100 MHz, DMSO- $d_6$ )  $\delta$  ppm: 131.4, 129.9, 126.9, 125.2, 119.5, 116.1, 111.1, 107.9, 68.4, 55.4, 47.6, 45.4, 42.1, 40.9, 30, 28.2, 25.7, 24.8, 18.7, 15.7, 13.5

**EXAMPLE 20** : [(2*R*,8*S*)-2,4,32-Trimethyl-28,28-dioxo-22,27-dioxa-28 $\lambda^6$ -thia-1,14,15,16-tetraazahexacyclo[21.5.3.1<sup>3,7</sup>.1<sup>9,13</sup>.0<sup>12,16</sup>.0<sup>26,30</sup>]tritriaconta-3(33),4,6,9(32),10,12,14,23,25,30-decaen-8-yl]acetic acid and [(2*R*,8*R*)-2,4,32-trimethyl-28,28-dioxo-22,27-dioxa-28 $\lambda^6$ -thia-1,14,15,16-tetraazahexacyclo[21.5.3.1<sup>3,7</sup>.1<sup>9,13</sup>.0<sup>12,16</sup>.0<sup>26,30</sup>]tritriaconta-3(33),4,6,9(32),10,12,14,23,25,30-decaen-8-yl]acetic acid

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**STEP 1 : Preparation of ethyl 3-{3-[(1S)-1-hydroxyethyl]-4-methylphenyl}-3-(1-{5-[(4-methoxyphenyl)methoxy]pentyl}-4-methyl-1H-benzotriazol-5-yl)propanoate**

5 Using General Procedure 6 starting from ethyl (2E)-3-(1-{5-[(4-methoxyphenyl)methoxy]pentyl}-4-methyl-1H-benzotriazol-5-yl)prop-2-enoate (1 eq.) and (1S)-1-[2-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]ethan-1-ol (2 eq.) as reactants, the title compound (77% yield) was obtained.

<sup>1</sup>H-NMR (400 MHz, DMSO-d<sub>6</sub>) δ ppm: 7.59 (d, 1 H), 7.45 (d, 1 H), 7.41 (d, 1 H), 7.18 (d, 2 H), 7.04 (dd, 1 H), 6.98 (d, 1 H), 6.87 (d, 2 H), 4.96 (d, 1 H), 4.82 (m, 1 H), 4.82 (m, 1 H), 4.62 (dd, 2 H), 4.31 (s, 2 H), 3.92 (q, 2 H), 3.73 (s, 3 H), 3.31 (m, 2 H), 3.15-3.09 (m, 2 H), 2.77 (s, 3 H), 2.19 (s, 3 H), 1.87 (m, 2 H), 1.51 (m, 2 H), 1.27 (m, 2 H), 1.23/1.21 (d, 3 H), 0.99 (t, 3 H)

**STEP 2 : Preparation of ethyl 3-(3-[(1R)-1-[6-(benzyloxy)-2,2-dioxo-2H-1,2λ<sup>6</sup>,3-benzoxathiazin-3(4H)-yl]ethyl]-4-methylphenyl)-3-(1-{5-[(4-methoxyphenyl)methoxy]pentyl}-4-methyl-1H-benzotriazol-5-yl)propanoate**

Using General Procedure 7 starting from ethyl 3-{3-[(1S)-1-hydroxyethyl]-4-methylphenyl}-3-(1-{5-[(4-methoxyphenyl)methoxy]pentyl}-4-methyl-1H-benzotriazol-5-yl)propanoate (1 eq.) and 6-(benzyloxy)-3,4-dihydro-2H-1,2λ<sup>6</sup>,3-benzoxathiazine-2,2-dione (1.5 eq.) as reactants, the title compound (64% yield) was obtained.

<sup>1</sup>H-NMR (400 MHz, DMSO-d<sub>6</sub>) δ ppm: 7.6 (d, 1 H), 7.51 (2d, 1 H), 7.5-6.8 (m, 15 H), 5.27 (q, 1 H), 5.09 (m, 2 H), 4.88 (m, 1 H), 4.59 (m, 2 H), 4.41 (m, 2 H), 4.29 (s, 2 H), 3.9 (q, 2 H),

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3.71 (s, 3 H), 3.29 (m, 2 H), 3.2 (m, 2 H), 2.76 (2s, 3 H), 2.28 (s, 3 H), 1.82 (m, 2 H), 1.49 (m, 2 H), 1.4 (m, 3 H), 1.22 (m, 2 H), 0.96 (m, 3 H)

**STEP 3 : Preparation of ethyl 3-{3-[(1*R*)-1-(6-hydroxy-2,2-dioxo-2*H*-1,2λ<sup>6</sup>,3-benzoxathiazin-3(4*H*)-yl)ethyl]-4-methylphenyl}-3-[1-(5-hydroxypentyl)-4-methyl-1*H*-benzotriazol-5-yl]propanoate**

Using General Procedure 8 starting from ethyl 3-{3-[(1*R*)-1-[6-(benzyloxy)-2,2-dioxo-2*H*-1,2λ<sup>6</sup>,3-benzoxathiazin-3(4*H*)-yl)ethyl]-4-methylphenyl}-3-[1-{5-[(4-methoxyphenyl)methoxy] pentyl}-4-methyl-1*H*-benzotriazol-5-yl]propanoate (1 eq.) as a reactant, the title compound (grey solid, 98% yield) was obtained.

**<sup>1</sup>H-NMR** (400 MHz, DMSO-d<sub>6</sub>) δ ppm: 9.63/9.62 (2m, 3 H), 7.62/7.56 (2dd, 2 H), 7.47/7.45 (2sl, 1 H), 7.1 (m, 2 H), 6.92/6.9 (2d, 1 H), 6.73 (m, 1 H), 6.58 (2d, 1 H), 5.25 (m, 1 H), 4.88 (m, 1 H), 4.63 (t, 2 H), 4.32 (m, 2 H), 3.94 (m, 2 H), 3.32 (m, 2 H), 3.22 (m, 2 H), 2.77 (s, 3 H), 2.28 (s, 3 H), 1.88 (m, 2 H), 1.46-1.37 (m+d, 5 H), 1.24 (m, 2 H), 1/0.99 (2t, 3 H)

**STEP 4 : Preparation of ethyl 3-[1-(5-bromopentyl)-4-methyl-1*H*-benzotriazol-5-yl]-3-{3-[(1*R*)-1-(6-hydroxy-2,2-dioxo-2*H*-1,2λ<sup>6</sup>,3-benzoxathiazin-3(4*H*)-yl)ethyl]-4-methylphenyl}propanoate**

Using General Procedure 9 starting from ethyl 3-{3-[(1*R*)-1-(6-hydroxy-2,2-dioxo-2*H*-1,2λ<sup>6</sup>,3-benzoxathiazin-3(4*H*)-yl)ethyl]-4-methylphenyl}-3-[1-(5-hydroxypentyl)-4-methyl-1*H*-benzotriazol-5-yl]propanoate (1 eq.) as a reactant, the title compound (white solid, 78% yield) was obtained.

**<sup>1</sup>H-NMR** (400 MHz, DMSO-d<sub>6</sub>) δ ppm: 9.6/9.59 (2s, 1 H), 7.62 (2d, 1 H), 7.58 (d, 1 H), 7.48/7.42 (2d, 1 H), 7.1 (m, 2 H), 6.9 (d, 1 H), 6.71 (m, 1 H), 6.59/6.55 (2d, 1 H), 5.26 (m, 1 H), 4.88 (m, 1 H), 4.65 (t, 2 H), 4.4-4.25 (m, 2 H), 3.93 (q, 2 H), 3.48 (t, 2 H), 3.21 (m, 2 H), 2.77 (s, 3 H), 2.28 (s, 3 H), 1.9 (m, 2 H), 1.8 (m, 2 H), 1.41 (2d, 3 H), 1.32 (m, 2 H), 1/0.99 (2t, 3 H)

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**STEP 5 : Preparation of ethyl [(2*R*)-2,4,32-trimethyl-28,28-dioxo-22,27-dioxa-28 $\lambda^6$ -thia-1,14,15,16-tetraazahexacyclo[21.5.3.1<sup>3,7</sup>.1<sup>9,13</sup>.0<sup>12,16</sup>.0<sup>26,30</sup>]tritriaconta-3(33),4,6,9(32),10,12,14,23,25,30-decaen-8-yl]acetate**

5 Using General Procedure 11 starting from ethyl 3-[1-(5-bromopentyl)-4-methyl-1*H*-benzotriazol-5-yl]-3-{3-[(1*R*)-1-(6-hydroxy-2,2-dioxo-2*H*-1,2 $\lambda^6$ ,3-benzoxathiazin-3(4*H*)-yl)ethyl]-4-methylphenyl}propanoate (1 eq.) as a reactant, the title compound (78% yield) was obtained.

<sup>1</sup>H-NMR (400 MHz, DMSO-d<sub>6</sub>)  $\delta$  ppm: 0.92 - 1.07 (m, 7 H) 1.27 - 1.53 (m, 9 H) 1.55 - 1.81  
 10 (m, 5 H) 1.85 - 1.98 (m, 3 H) 1.99 - 2.09 (m, 2 H) 2.23 - 2.36 (m, 7 H) 2.75 (s, 4 H) 2.80 (s, 3 H) 2.94 (dd, J=15.71, 7.52 Hz, 1 H) 3.10 (dd, J=16.08, 7.03 Hz, 2 H) 3.21 - 3.29 (m, 2 H) 3.57 - 3.78 (m, 3 H) 3.80 - 3.98 (m, 8 H) 4.04 - 4.21 (m, 2 H) 4.56 - 4.76 (m, 4 H) 4.81 - 4.89 (m, 1 H) 4.95 (t, J=7.82 Hz, 1 H) 5.21 - 5.36 (m, 2 H) 5.99 (s, 2 H) 6.76 - 6.88 (m, 3 H) 6.91 - 6.99 (m, 2 H) 7.13 (dd, J=10.51, 8.19 Hz, 2 H) 7.24 - 7.38 (m, 3 H) 7.48 (d, J=7.95 Hz, 1 H) 7.60 -  
 15 7.71 (m, 2 H) 7.84 (d, J=8.68 Hz, 1 H)

**STEP 6 : Preparation of EXAMPLE 20**

Using General Procedure 12 starting from ethyl [(2*R*)-2,4,32-trimethyl-28,28-dioxo-22,27-  
 20 dioxa-28 $\lambda^6$ -thia-1,14,15,16-tetraazahexacyclo[21.5.3.1<sup>3,7</sup>.1<sup>9,13</sup>.0<sup>12,16</sup>.0<sup>26,30</sup>]tritriaconta-3(33),4,6,9(32),10,12,14,23,25,30-decaen-8-yl]acetate (1 eq.) as a reactant, the title compound (white solid, 32% yield) was obtained.

The diastereo-pure products were obtained by chromatographic separation on chiral column.

25 **Example 20a (2*R*,8*S*)**

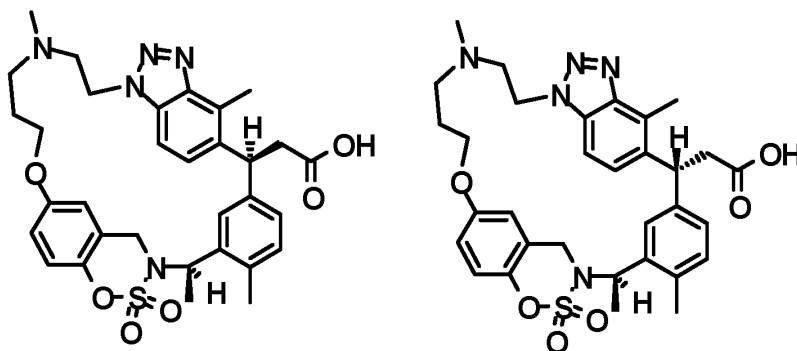
**HRMS** calculated for C<sub>31</sub>H<sub>34</sub>N<sub>4</sub>O<sub>6</sub>S: 590.2199; [M+H]<sup>+</sup> found: 591.2273 ( $\delta$ =0.2 ppm)

<sup>1</sup>H-NMR (400 MHz, DMSO-d<sub>6</sub>)  $\delta$  ppm: 12.4-11.9 (m, 1 H), 7.62 (d, 1 H), 7.49 (dd, 1 H), 7.31 (d, 1 H), 7.09 (d, 1 H), 6.94 (d, 1 H), 6.84 (d, 1 H), 6.81 (dd, 1 H), 5.99 (d, 1 H), 5.28 (q, 1 H), 4.91 (m, 1 H), 4.75-4.6 (t, 2 H), 4.08/3.7 (m, 2 H), 3.89/3.7 (m, 2 H), 3.16/2.8 (2m, 2 H), 2.8 (s,  
 30 3 H), 2.32 (s, 3 H), 2.1-1.85 (m, 2 H), 1.69 (m, 2 H), 1.55-1.23 (m, 2 H), 1.12 (d, 3 H)

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**Example 20b (2R,8R)****HRMS** calculated for  $C_{31}H_{34}N_4O_6S$ : 590.2199;  $[M+H]^+$  found: 591.2274 ( $\delta=0.4$  ppm)

**$^1H$ -NMR** (400 MHz, DMSO- $d_6$ )  $\delta$  ppm: 12.4-11.9 (m, 1 H), 7.81 (d, 1 H), 7.68 (d, 1 H), 7.37 (dd, 1 H), 7.29 (d, 1 H), 7.13 (d, 1 H), 6.98 (d, 1 H), 6.83 (dd, 1 H), 5.97 (d, 1 H), 5.3 (q, 1 H), 4.81 (m, 1 H), 4.7 (t, 2 H), 4.15/3.6 (m, 2 H), 3.85 (m, 2 H), 3.18/2.99 (2m, 2 H), 2.71 (s, 3 H), 2.29 (s, 3 H), 2.1-1.85 (m, 2 H), 1.8-1.55 (m, 2 H), 1.5-1.2 (m, 5 H)

**EXAMPLE 21 : [(2R,8S)-2,4,19,33-Tetramethyl-29,29-dioxo-23,28-dioxa-29 $\lambda^6$ -thia-**10 **1,14,15,16,19-****pentaazahexacyclo[22.5.3.1<sup>3,7</sup>.1<sup>9,13</sup>.0<sup>12,16</sup>.0<sup>27,31</sup>]tetratriaconta-****3(34),4,6,9(33),10,12,14,24,26,31-decaen-8-yl]acetic acid and****[(2R,8R)-2,4,19,33-tetramethyl-29,29-dioxo-23,28-dioxa-29 $\lambda^6$ -thia-****1,14,15,16,19-**15 **pentaazahexacyclo[22.5.3.1<sup>3,7</sup>.1<sup>9,13</sup>.0<sup>12,16</sup>.0<sup>27,31</sup>]tetratriaconta-****3(34),4,6,9(33),10,12,14,24,26,31-decaen-8-yl]acetic acid**

**STEP A1 : Preparation of *tert*-butyl (2-[(3-(benzyloxy)propyl](methyl)amino}ethyl) carbamate**

20

To a solution of [(3-bromopropoxy)methyl]benzene (10 g, 43.6 mmol, 7.7 mL) in MeCN (3 mL/mmol, 131 mL) *tert*-butyl [2-(methylamino)ethyl]carbamate (1 eq., 7.61 g, 43.6 mmol) and

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K<sub>2</sub>CO<sub>3</sub> (2 eq., 8.65 g, 87.3 mmol) were added at RT. The reaction mixture was heated to 50 °C and stirred for 2 h. After completion of the reaction the mixture was diluted with 500 ml of EtOAc, extracted with 500 ml of water, then with 500 ml of brine. The organic layer was dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>, filtered, concentrated to dryness to give the crude product as a colorless oil, which was used in a next step without further purification (14 g, 99% yield).

<sup>1</sup>H-NMR (400 MHz, DMSO-d<sub>6</sub>) δ ppm: 7.38-7.28 (m, 5 H), 6.58 (t, 1 H), 4.43 (s, 2 H), 3.45 (t, 2 H), 2.99 (q, 2 H), 2.38 (t, 2 H), 2.32 (t, 2 H), 2.13 (s, 3 H), 1.65 (quint, 2 H), 1.37 (s, 9 H)

#### STEP A2 : Preparation of *N*<sup>1</sup>-[3-(benzyloxy)propyl]-*N*<sup>1</sup>-methylethane-1,2-diamine

10

To a solution of *tert*-butyl (2-{[3-(benzyloxy)propyl](methyl)amino} ethyl)carbamate (14 g, 43 mmol) in dioxane (5 mL/mmol, 220 mL) HCl (4N in dioxane) (4 eq., 43 mL) was added at RT and the reaction mixture was stirred overnight. After completion of the reaction the volatiles were evaporated to dryness under reduced pressure. The crude product was partitioned between 200 mL DCM and 300 ml sat. aq. NaHCO<sub>3</sub>. The layers were separated, the aq. layer was evaporated to dryness under reduced pressure. 50 ml of MeCN was added, then the solid was filtered-off and washed with 2x20 ml MeCN. The mother liquor was concentrated to dryness to give the crude product as a yellow oil. The crude product was used without further purification (6.2 g, 62% yield).

<sup>1</sup>H-NMR (400 MHz, DMSO-d<sub>6</sub>) δ ppm: 7.38-7.23 (m, 5 H), 4.44 (s, 2 H), 3.45 (t, 2 H), 2.56 (t, 2 H), 2.36 (t, 2 H), 2.33 (t, 2 H), 2.1 (s, 3 H), 1.67 (quint, 2 H)

#### STEP A3 : Preparation of *N*<sup>1</sup>-[3-(benzyloxy)propyl]-*N*<sup>1</sup>-methyl-*N*<sup>2</sup>-(3-methyl-2-nitrophenyl)ethane-1,2-diamine

25

Using General Procedure 2 STEP 1 starting from 1-fluoro-3-methyl-2-nitro-benzene (1 eq.) and the crude *N*<sup>1</sup>-[3-(benzyloxy)propyl]-*N*<sup>1</sup>-methylethane-1,2-diamine (1.2 eq.) as reactants, the title compound (58% yield) was obtained.

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**<sup>1</sup>H-NMR** (400 MHz, DMSO-d<sub>6</sub>) δ ppm: 7.35-7.22 (m, 1 H), 7.35-7.22 (m, 5 H), 6.78 (d, 1 H), 6.61 (t, 1 H), 6.58 (d, 1 H), 4.41 (s, 2 H), 3.49 (t, 2 H), 3.2 (q, 2 H), 2.55 (t, 2 H), 2.41 (t, 2 H), 2.32 (s, 3 H), 2.19 (s, 3 H), 1.69 (quint, 2 H)

5     **STEP A4 : Preparation of *N*<sup>1</sup>-(2-{[3-(benzyloxy)propyl](methyl)amino}ethyl)-4-bromo-3-methylbenzene-1,2-diamine**

Using General Procedure 2 STEP 2 starting from *N*<sup>1</sup>-[3-(benzyloxy)propyl]-*N*<sup>1</sup>-methyl-*N*<sup>2</sup>-(3-methyl-2-nitrophenyl)ethane-1,2-diamine (1 eq.) as a reactant, *N*<sup>1</sup>-[3-(benzyloxy)propyl]-*N*<sup>2</sup>-(4-bromo-3-methyl-2-nitrophenyl)-*N*<sup>1</sup>-methylethane-1,2-diamine (71% yield) was obtained. The  
10     crude product was reacted using General Procedure 2 STEP 3 resulting the title compound (76% yield).

**LC-MS** calculated for C<sub>20</sub>H<sub>28</sub>BrN<sub>3</sub>O: 405; [M+H]<sup>+</sup> found: 406/408

15     **STEP A5 : Preparation of 3-(benzyloxy)-*N*-[2-(5-bromo-4-methyl-1*H*-benzotriazol-1-yl)ethyl]-*N*-methylpropan-1-amine**

Using General Procedure 2 STEP 4 starting from *N*<sup>1</sup>-(2-{[3-(benzyloxy)propyl](methyl)amino}ethyl)-4-bromo-3-methylbenzene-1,2-diamine (1 eq.) as a reactant, the title  
20     compound (85% yield) was obtained.

**<sup>1</sup>H-NMR** (400 MHz, DMSO-d<sub>6</sub>) δ ppm: 8.19 (s, 1 H), 7.4 (2d, 2 H), 7.3 (t, 2 H), 7.25 (t, 1 H), 7.2 (d, 2 H), 4.3 (t, 2 H), 4.22 (s, 2 H), 3.18 (t, 2 H), 2.68 (t, 2 H), 2.55 (s, 3 H), 2.35 (t, 2 H), 2.2 (s, 3 H), 1.5 (m, 2 H)

25     **STEP A6 : Preparation of ethyl (2*E*)-3-[1-(2-{[3-(benzyloxy)propyl](methyl)amino}ethyl)-4-methyl-1*H*-benzotriazol-5-yl]prop-2-enoate**

Using General Procedure 2 STEP 5 starting from 3-(benzyloxy)-*N*-[2-(5-bromo-4-methyl-1*H*-benzotriazol-1-yl)ethyl]-*N*-methylpropan-1-amine (1 eq.) as a reactant, the title compound  
30     (93% yield) was obtained.

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<sup>1</sup>H-NMR (400 MHz, DMSO-d<sub>6</sub>) δ ppm: 8 (d, 1 H), 7.91 (d, 1 H), 7.7 (d, 1 H), 7.3 (t, 2 H), 7.22 (t, 1 H), 7.19 (d, 2 H), 6.61 (d, 1 H), 4.77 (t, 2 H), 4.2 (q, 2 H), 4.18 (s, 2 H), 3.08 (t, 2 H), 2.82 (t, 2 H), 2.79 (s, 3 H), 2.31 (t, 2 H), 2.19 (s, 3 H), 1.42 (q, 2 H), 1.28 (t, 3 H)

5 **STEP 1 : Preparation of ethyl 3-[1-(2-{[3-(benzyloxy)propyl](methyl)amino}ethyl)-4-methyl-1*H*-benzotriazol-5-yl]-3-{3-[(1*S*)-1-hydroxyethyl]-4-methylphenyl}propanoate**

Using General Procedure 6 starting from ethyl (2*E*)-3-[1-(2-{[3-(benzyloxy)propyl]  
10 (methyl)amino}ethyl)-4-methyl-1*H*-benzotriazol-5-yl]prop-2-enoate (1 eq.) and (1*S*)-1-[2-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]ethanol (1 eq.) as reactants, the title compound (33% yield) was obtained.

<sup>1</sup>H-NMR (400 MHz, DMSO-d<sub>6</sub>) δ ppm: 7.59 (d, 1 H), 7.45 (d, 1 H), 7.41 (m, 1 H), 7.35 (d, 1 H), 7.31 (dd, 1 H), 7.22 (m, 2 H), 7.02 (m, 1 H), 6.97 (m, 2 H), 4.93 (d, 1 H), 4.82 (m, 1 H),  
15 4.82 (m, 1 H), 4.7 (t, 2 H), 4.22 (s, 2 H), 3.91 (q, 2 H), 3.15 (m, 2 H), 3.15-3.05 (m, 2 H), 2.82 (t, 2 H), 2.75 (s, 3 H), 2.35 (t, 2 H), 2.19 (s, 3 H), 2.19 (s, 3 H), 1.47 (quint, 2 H), 1.21 (d, 3 H), 0.99 (t, 3 H)

20 **STEP 2 : Preparation of ethyl 3-(3-{(1*R*)-1-[6-(benzyloxy)-2,2-dioxo-2*H*-1,2λ<sup>6</sup>,3-benzoxathiazin-3(4*H*)-yl]ethyl}-4-methylphenyl)-3-[1-(2-{[3-(benzyloxy)propyl] (methyl)amino}ethyl)-4-methyl-1*H*-benzotriazol-5-yl]propanoate**

Using General Procedure 7 starting from ethyl 3-[1-[2-[3-benzyloxypropyl(methyl)amino]ethyl]-4-methyl-benzotriazol-5-yl]-3-[3-[(1*S*)-1-hydroxyethyl]-4-methyl-phenyl]propanoate (1 eq.) and 6-(benzyloxy)-3,4-dihydro-2*H*-1,2λ<sup>6</sup>,3-benzoxathiazine-2,2-dione (1.1 eq.) as reactants, the title compound (58% yield) was obtained.  
LC-MS calculated for C<sub>48</sub>H<sub>55</sub>N<sub>5</sub>O<sub>7</sub>S: 845; [M+H]<sup>+</sup> found: 846



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**STEP 3 : Preparation of ethyl 3-{3-[(1*R*)-1-(6-hydroxy-2,2-dioxo-2*H*-1,2λ<sup>6</sup>,3-benzoxathiazin-3(4*H*)-yl)ethyl]-4-methylphenyl}-3-(1-{2-[(3-hydroxypropyl)(methyl)amino]ethyl}-4-methyl-1*H*-benzotriazol-5-yl)propanoate**

5

Using General Procedure 8 starting from ethyl 3-{3-[(1*R*)-1-[6-(benzyloxy)-2,2-dioxo-2*H*-1,2λ<sup>6</sup>,3-benzoxathiazin-3(4*H*)-yl]ethyl]-4-methylphenyl}-3-[1-(2-{[3-(benzyloxy)propyl](methyl)amino}ethyl)-4-methyl-1*H*-benzotriazol-5-yl]propanoate (1 eq.) as a reactant, the title compound (yellow oil, 97% yield) was obtained.

10 **LC-MS** calculated for C<sub>34</sub>H<sub>43</sub>N<sub>5</sub>O<sub>7</sub>S: 665; [M+H]<sup>+</sup> found: 666

**STEP 4 : Preparation of ethyl 3-(1-{2-[(3-bromopropyl)(methyl)amino]ethyl}-4-methyl-1*H*-benzotriazol-5-yl)-3-{3-[(1*R*)-1-(6-hydroxy-2,2-dioxo-2*H*-1,2λ<sup>6</sup>,3-benzoxathiazin-3(4*H*)-yl)ethyl]-4-methylphenyl}propanoate**

15

Using General Procedure 9 starting from ethyl 3-{3-[(1*R*)-1-(6-hydroxy-2,2-dioxo-2*H*-1,2λ<sup>6</sup>,3-benzoxathiazin-3(4*H*)-yl)ethyl]-4-methylphenyl}-3-(1-{2-[(3-hydroxypropyl)(methyl)amino]ethyl}-4-methyl-1*H*-benzotriazol-5-yl)propanoate (1 eq.) as a reactant, the title compound (white solid, 20% yield) was obtained.

20 **LC-MS** calculated for C<sub>34</sub>H<sub>42</sub>BrN<sub>5</sub>O<sub>6</sub>S: 727; [M+H]<sup>+</sup> found: 728/730

**STEP 5 : Preparation of ethyl [(2*R*)-2,4,19,33-tetramethyl-29,29-dioxo-23,28-dioxa-29λ<sup>6</sup>-thia-1,14,15,16,19-pentaazahexacyclo[22.5.3.1<sup>3,7</sup>.1<sup>9,13</sup>.0<sup>12,16</sup>.0<sup>27,31</sup>]tetratriaconta-3(34),4,6,9(33),10,12,14,24,26,31-decaen-8-yl]acetate**

25

Using General Procedure 11 starting from ethyl 3-(1-{2-[(3-bromopropyl)(methyl)amino]ethyl}-4-methyl-1*H*-benzotriazol-5-yl)-3-{3-[(1*R*)-1-(6-hydroxy-2,2-dioxo-2*H*-1,2λ<sup>6</sup>,3-benzoxathiazin-3(4*H*)-yl)ethyl]-4-methylphenyl}propanoate (1 eq.) as a reactant, the title compound (white solid, 99% yield) was obtained.

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**<sup>1</sup>H-NMR** (400 MHz, DMSO-d<sub>6</sub>) δ ppm: 7.74/7.63 (2d, 1 H), 7.73/7.48 (2d, 1 H), 7.58 (s, 1 H), 7.27/7.04 (2d, 1 H), 7.25/7.12 (d, 1 H), 7.01/6.93 (2d, 1 H), 6.84/6.73 (2d, 1 H), 6.37/5.81 (2sl, 1 H), 5.35/5.29 (2q, 1 H), 4.93/4.87 (2t, 1 H), 4.8/4.71/4.61/4.58 (4m, 2 H), 4.24/4.02/3.98/3.87 (4d, 2 H), 3.91 (q, 2 H), 3.83 (m, 2 H), 3.34-3.13/3.02 (4dd, 2 H), 3.11/3.06/2.86/2.72 (4m, 2 H), 2.84 (2s, 3 H), 2.59-2.46/2.4 (2m, 2 H), 2.29 (s, 3 H), 2.19/2.13 (2sl, 3 H), 1.85 (m, 2 H), 1.52/1.27 (2d, 3 H), 1.01 (2d, 3 H)

**STEP 6 : Preparation of EXAMPLE 21**

Using General Procedure 12 starting from ethyl [(2*R*)-2,4,19,33-tetramethyl-29,29-dioxo-23,28-dioxa-29λ<sup>6</sup>-thia-1,14,15,16,19-pentaazahexacyclo[22.5.3.1<sup>3,7</sup>.1<sup>9,13</sup>.0<sup>12,16</sup>.0<sup>27,31</sup>]tetratriaconta-3(34),4,6,9(33),10,12,14,24,26,31-decaen-8-yl]acetate (1 eq.) as a reactant, the title compound (white solid, 83% yield) was obtained.

The diastereo-pure products were obtained by chromatographic separation on chiral column.

**Example 21a (2*R*,8*S*)**

**HRMS** calculated for C<sub>32</sub>H<sub>37</sub>N<sub>5</sub>O<sub>6</sub>S: 619.2464; [M+H]<sup>+</sup> found: 620.2538 (δ=0.1 ppm)

**<sup>1</sup>H-NMR** (400 MHz, DMSO-d<sub>6</sub>) δ ppm: 12.05 (m, 1 H), 7.71 (m, 2 H), 7.55 (d, 1 H), 7.29 (dd, 1 H), 7.12 (d, 1 H), 7 (d, 1 H), 6.81 (dd, 1 H), 6.38 (d, 1 H), 5.35 (q, 1 H), 4.85 (t, 1 H), 4.78/4.58 (2m, 2 H), 4.21/3.95 (2d, 2 H), 3.82 (m, 2 H), 3.1/3 (2dd, 2 H), 3.05/2.7 (2m, 2 H), 2.81 (s, 3 H), 2.55 (m, 2 H), 2.3 (s, 3 H), 2.15 (s, 3 H), 1.82 (m, 2 H), 1.5 (d, 3 H)

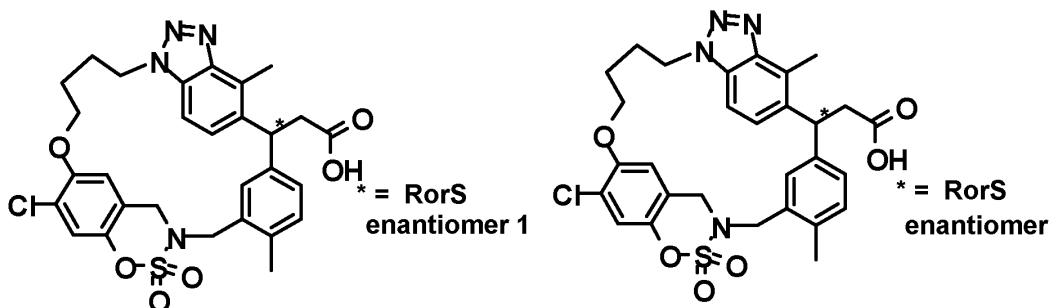
**Example 21b (2*R*,8*R*)**

**HRMS** calculated for C<sub>32</sub>H<sub>37</sub>N<sub>5</sub>O<sub>6</sub>S: 619.2464; [M+H]<sup>+</sup> found: 620.2576 (δ=6.2 ppm)

**<sup>1</sup>H-NMR** (400 MHz, DMSO-d<sub>6</sub>) δ ppm: 12.3 (m, 1 H), 7.65/7.22 (2d, 2 H), 7.5 (dd, 1 H), 7.22 (d, 1 H), 7 (d, 1 H), 6.95 (d, 1 H), 6.72 (dd, 1 H), 5.82 (d, 1 H), 5.3 (q, 1 H), 4.91 (t, 1 H), 4.7/4.6 (2m, 2 H), 4.02/3.85 (2d, 2 H), 3.48/3.32 (2m, 2 H), 3.1 (m, 2 H), 2.88 (m, 2 H), 2.81 (s, 3 H), 2.4 (t, 2 H), 2.3 (s, 3 H), 2.2 (s, 3 H), 1.68 (m, 2 H), 1.25 (d, 3 H)

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**EXAMPLE 22 :** [23-Chloro-4,31-dimethyl-27,27-dioxo-21,26-dioxa-27 $\lambda^6$ -thia-1,14,15,16-tetraazahexacyclo[20.5.3.1<sup>3,7</sup>.1<sup>9,13</sup>.0<sup>12,16</sup>.0<sup>25,29</sup>]dotriaconta-3(32),4,6,9(31),10,12,14,22,24,29-decaen-8-yl]acetic acid



5

**STEP C1 : Preparation of 5-(benzyloxy)-4-chloro-2-hydroxybenzaldehyde**

Using General Procedure 4 STEP 1 starting from 4-(benzyloxy)-3-chlorophenol (1 eq.) as a reactant, the title compound (45% yield) was obtained.

10 **<sup>1</sup>H-NMR** (500 MHz, DMSO-d<sub>6</sub>)  $\delta$  ppm: 10.66 (s, 1 H), 10.22 (s, 1 H), 7.49-7.3 (m, 5 H), 7.38 (s, 1 H), 7.12 (s, 1 H), 5.16 (s, 2 H)

**STEP C2 : Preparation of 6-(benzyloxy)-7-chloro-2H-1,2 $\lambda^6$ ,3-benzoxathiazine-2,2-dione**

15 Using General Procedure 4 STEP 2 starting from 5-(benzyloxy)-4-chloro-2-hydroxybenzaldehyde (1 eq.) as a reactant, the title compound (91% yield) was obtained.

**<sup>1</sup>H-NMR** (500 MHz, DMSO-d<sub>6</sub>)  $\delta$  ppm: 9.16 (s, 1 H), 7.93 (s, 1 H), 7.92 (s, 1 H), 7.53-7.34 (m, 5 H), 5.28 (s, 2 H)

20 **STEP C3 : Preparation of 6-(benzyloxy)-7-chloro-3,4-dihydro-2H-1,2 $\lambda^6$ ,3-benzoxathiazine-2,2-dione**

Using General Procedure 4 STEP 3 starting from 6-(benzyloxy)-7-chloro-2H-1,2 $\lambda^6$ ,3-benzoxathiazine-2,2-dione (1 eq.) as a reactant, the title compound (quant.) was obtained.

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<sup>1</sup>H-NMR (500 MHz, DMSO-d<sub>6</sub>) δ ppm: 8.5 (br., 1 H), 7.47 (dm, 2 H), 7.41 (tm, 2 H), 7.35 (tm, 1 H), 7.34 (s, 1 H), 7.25 (s, 1 H), 5.17 (s, 2 H), 4.52 (s, 2 H)

**STEP 1 : Preparation of ethyl 3-(3-{[6-(benzyloxy)-7-chloro-2,2-dioxo-2*H*-1,2λ<sup>6</sup>,3-benzoxathiazin-3(4*H*)-yl]methyl}-4-methylphenyl)-3-(1-{4-[(4-methoxyphenyl)methoxy]butyl}-4-methyl-1*H*-benzotriazol-5-yl)propanoate**

Using General Procedure 7 starting from ethyl 3-[3-(hydroxymethyl)-4-methylphenyl]-3-(1-{4-[(4-methoxyphenyl)methoxy]butyl}-4-methyl-1*H*-benzotriazol-5-yl)propanoate (1 eq.) and 6-(benzyloxy)-7-chloro-3,4-dihydro-2*H*-1,2λ<sup>6</sup>,3-benzoxathiazine-2,2-dione (1.4 eq.) as reactants, the title compound (yellow oil, 50% yield) was obtained.

<sup>1</sup>H-NMR (500 MHz, DMSO-d<sub>6</sub>) δ ppm: 7.57 (d, 1 H), 7.51-7.33 (m, 5 H), 7.48 (d, 1 H), 7.45 (s, 1 H), 7.26 (s, 1 H), 7.26 (d, 1 H), 7.19 (dd, 1 H), 7.18 (dm, 2 H), 7.13 (d, 1 H), 6.86 (dm, 2 H), 5.16 (s, 2 H), 4.85 (t, 1 H), 4.62 (t, 2 H), 4.49/4.44 (d+d, 2 H), 4.29 (s, 2 H), 4.27/4.21 (d+d, 2 H), 3.91 (q, 2 H), 3.72 (s, 3 H), 3.35 (t, 2 H), 3.2/3.16 (dd+dd, 2 H), 2.77 (s, 3 H), 2.2 (s, 3 H), 1.89 (m, 2 H), 1.45 (m, 2 H), 0.96 (t, 3 H)

**STEP 2 : Preparation of ethyl 3-{3-[(7-chloro-6-hydroxy-2,2-dioxo-2*H*-1,2λ<sup>6</sup>,3-benzoxathiazin-3(4*H*)-yl)methyl]-4-methylphenyl}-3-[1-(4-hydroxybutyl)-4-methyl-1*H*-benzotriazol-5-yl]propanoate**

Using General Procedure 8 starting from ethyl 3-[3-[(6-benzyloxy-7-chloro-2,2-dioxo-4*H*-1,2λ<sup>6</sup>,3-benzoxathiazin-3-yl)methyl]-4-methylphenyl]-3-[1-[4-[(4-methoxyphenyl)methoxy]butyl]-4-methyl-benzotriazol-5-yl]propanoate (1 eq.) as a reactant, the title compound (yellow oil, 74% yield) was obtained.

<sup>1</sup>H-NMR (500 MHz, DMSO-d<sub>6</sub>) δ ppm: 10.48 (brs, 1 H), 7.61 (d, 1 H), 7.51 (d, 1 H), 7.31 (s, 1 H), 7.27 (d, 1 H), 7.19 (dd, 1 H), 7.13 (d, 1 H), 6.85 (s, 1 H), 4.83 (t, 1 H), 4.64 (t, 2 H), 4.45/4.42 (d+d, 2 H), 4.43 (brs, 1 H), 4.25/4.2 (d+d, 2 H), 3.93 (q, 2 H), 3.37 (t, 2 H), 3.17 (d, 2 H), 2.76 (s, 3 H), 2.22 (s, 3 H), 1.9 (m, 2 H), 1.35 (m, 2 H), 0.99 (t, 3 H)

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**STEP 3 : Preparation of ethyl [23-chloro-4,31-dimethyl-27,27-dioxo-21,26-dioxa-27 $\lambda^6$ -thia-1,14,15,16-tetraazahexacyclo[20.5.3.1<sup>3,7</sup>.1<sup>9,13</sup>.0<sup>12,16</sup>.0<sup>25,29</sup>]dotriaconta-3(32),4,6,9(31),10,12,14,22,24,29-decaen-8-yl]acetate**

5 Using General Procedure 10 starting from ethyl 3-{3-[(7-chloro-6-hydroxy-2,2-dioxo-2*H*-1,2 $\lambda^6$ ,3-benzoxathiazin-3(4*H*)-yl)methyl]-4-methylphenyl}-3-[1-(4-hydroxybutyl)-4-methyl-1*H*-benzotriazol-5-yl]propanoate (1 eq.) as a reactant, ethyl 3-[1-(4-chlorobutyl)-4-methyl-1*H*-benzotriazol-5-yl]-3-{3-[(7-chloro-6-hydroxy-2,2-dioxo-2*H*-1,2 $\lambda^6$ ,3-benzoxathiazin-3(4*H*)-yl)methyl]-4-methylphenyl}propanoate (yellow solid foam, quant.) was obtained, which was  
10 reacted in the next step without further purification using General Procedure 11. The title compound (white solid) was obtained (64% yield).

<sup>1</sup>H-NMR (500 MHz, DMSO-d<sub>6</sub>)  $\delta$  ppm: 7.68 (d, 1 H), 7.47 (dd, 1 H), 7.47 (d, 1 H), 7.35 (s, 1 H), 7.27 (d, 1 H), 6.67 (d, 1 H), 6.1 (s, 1 H), 4.85/4.74 (dm+dm, 2 H), 4.77 (t, 1 H), 4.27/3.9 (d+d, 2 H), 4/3.76 (d+d, 2 H), 3.92 (q, 2 H), 3.7/3.44 (m+m, 2 H), 3.13/3.06 (dd+dd, 2 H),  
15 2.64 (s, 3 H), 2.31 (s, 3 H), 2.22/1.99 (m+m, 2 H), 1.82/1.62 (m+m, 2 H), 1.01 (t, 3 H)

**STEP 4 : Preparation of [23-chloro-4,31-dimethyl-27,27-dioxo-21,26-dioxa-27 $\lambda^6$ -thia-1,14,15,16-tetraazahexacyclo[20.5.3.1<sup>3,7</sup>.1<sup>9,13</sup>.0<sup>12,16</sup>.0<sup>25,29</sup>]dotriaconta-3(32),4,6,9(31),10,12,14,22,24,29-decaen-8-yl]acetic acid**

20

Using General Procedure 12 starting from ethyl [23-chloro-4,31-dimethyl-27,27-dioxo-21,26-dioxa-27 $\lambda^6$ -thia-1,14,15,16-tetraazahexacyclo[20.5.3.1<sup>3,7</sup>.1<sup>9,13</sup>.0<sup>12,16</sup>.0<sup>25,29</sup>]dotriaconta-3(32),4,6,9(31),10,12,14,22,24,29-decaen-8-yl]acetate (1 eq.) as a reactant, the title compound (white solid, 94% yield) was obtained.

25 The enantiopure products were obtained by chromatographic separation on chiral column.

**Example 22a (E1)**

HRMS calculated for C<sub>29</sub>H<sub>29</sub>ClN<sub>4</sub>O<sub>6</sub>S: 596.1497; [M+H]<sup>+</sup> found: 597.1564 ( $\delta$  = -0.9 ppm)

30 **Example 22b (E2)**

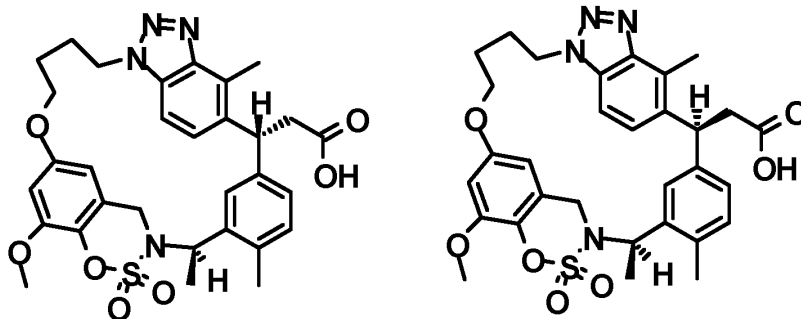
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**HRMS** calculated for  $C_{29}H_{29}ClN_4O_6S$ : 596.1497;  $[M+H]^+$  found: 597.1549 ( $\delta = -3.4$  ppm)

**$^1H$ -NMR** (500 MHz, DMSO- $d_6$ )  $\delta$  ppm: 12.23 (brs, 1 H), 7.68 (d, 1 H), 7.48 (dd, 1 H), 7.46 (d, 1 H), 7.35 (s, 1 H), 7.27 (d, 1 H), 6.65 (d, 1 H), 6.09 (s, 1 H), 4.85/4.74 (m+m, 2 H), 4.75 (m, 1 H), 4.26/3.91 (d+d, 2 H), 4.01/3.77 (d+d, 2 H), 3.69/3.42 (m+m, 2 H), 3.02/2.96 (dd+dd, 2 H), 2.64 (s, 3 H), 2.31 (s, 3 H), 2.22/2.01 (m+m, 2 H), 1.83/1.63 (m+m, 2 H)

**$^{13}C$ -NMR** (125 MHz, DMSO- $d_6$ )  $\delta$  ppm: 131.3, 131.2, 128.7, 127.2, 120.1, 111.5, 107.9, 68.7, 52.1, 48.7, 48.1, 41.8, 40.9, 26.7, 25.5, 18.5, 13.4

**EXAMPLE 23** : [(2*R*,8*R*)-24-Methoxy-2,4,31-trimethyl-27,27-dioxo-21,26-dioxo-27 $\lambda^6$ -thia-1,14,15,16-tetraazahexacyclo[20.5.3.1<sup>3,7</sup>.1<sup>9,13</sup>.0<sup>12,16</sup>.0<sup>25,29</sup>]dotriaconta-3(32),4,6,9(31),10,12,14,22,24,29-decaen-8-yl]acetic acid and [(2*R*,8*S*)-24-methoxy-2,4,31-trimethyl-27,27-dioxo-21,26-dioxo-27 $\lambda^6$ -thia-1,14,15,16-tetraazahexacyclo[20.5.3.1<sup>3,7</sup>.1<sup>9,13</sup>.0<sup>12,16</sup>.0<sup>25,29</sup>]dotriaconta-3(32),4,6,9(31),10,12,14,22,24,29-decaen-8-yl]acetic acid



**STEP 1** : Preparation of ethyl 3-(3-((1*R*)-1-[6-(benzyloxy)-8-methoxy-2,2-dioxo-2*H*-1,2 $\lambda^6$ ,3-benzoxathiazin-3(4*H*)-yl]ethyl)-4-methylphenyl)-3-(1-{4-[(4-methoxyphenyl)methoxy]butyl}-4-methyl-1*H*-benzotriazol-5-yl)propanoate

Using General Procedure 7 starting from ethyl 3-{3-[(1*R*)-1-hydroxyethyl]-4-methylphenyl}-3-(1-{4-[(4-methoxyphenyl)methoxy]butyl}-4-methyl-1*H*-benzotriazol-5-yl)propanoate (1 eq.)

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and 6-(benzyloxy)-8-methoxy-3,4-dihydro-2*H*-1,2λ<sup>6</sup>,3-benzoxathiazine-2,2-dione (1.05 eq.) as reactants, the title compound (79% yield) was obtained.

**<sup>1</sup>H-NMR** (400 MHz, DMSO-d<sub>6</sub>) δ ppm: 0.88 - 1.05 (m, 14 H) 1.13 - 1.30 (m, 10 H) 1.36 - 1.49 (m, 20 H) 1.82 - 1.94 (m, 9 H) 2.27 (s, 11 H) 2.74 - 2.81 (m, 11 H) 3.12 - 3.26 (m, 8 H) 3.34 (q, J=6.15 Hz, 8 H) 3.72 (s, 13 H) 3.81 (s, 11 H) 3.92 (q, J=7.09 Hz, 8 H) 4.23 - 4.36 (m, 11 H) 4.39 (s, 4 H) 4.55 - 4.65 (m, 8 H) 4.87 (t, J=7.76 Hz, 4 H) 5.01 - 5.14 (m, 7 H) 5.21 - 5.30 (m, 3 H) 6.35 (d, J=2.57 Hz, 1 H) 6.42 (d, J=2.57 Hz, 1 H) 6.72 - 6.78 (m, 1 H) 6.86 (d, J=8.56 Hz, 2 H) 7.07 - 7.14 (m, 2 H) 7.17 (d, J=8.56 Hz, 2 H) 7.28 - 7.38 (m, 1 H) 7.38 - 7.44 (m, 3 H) 7.44 - 7.49 (m, 2 H) 7.49 - 7.55 (m, 1 H) 7.56 - 7.62 (m, 1 H)

10

**STEP 2 : Preparation of ethyl 3-[1-(4-hydroxybutyl)-4-methyl-1*H*-benzotriazol-5-yl]-3-{3-[(1*R*)-1-(6-hydroxy-8-methoxy-2,2-dioxo-2*H*-1,2λ<sup>6</sup>,3-benzoxathiazin-3(4*H*)-yl)ethyl]-4-methylphenyl}propanoate**

15 Using General Procedure 8 starting from ethyl 3-(3-{(1*R*)-1-[6-(benzyloxy)-8-methoxy-2,2-dioxo-2*H*-1,2λ<sup>6</sup>,3-benzoxathiazin-3(4*H*)-yl]ethyl}-4-methylphenyl)-3-(1-{4-[(4-methoxyphenyl)methoxy]butyl}-4-methyl-1*H*-benzotriazol-5-yl)propanoate (1 eq.) as a reactant, the title compound (yellow solid, 98% yield) was obtained.

**<sup>1</sup>H-NMR** (400 MHz, DMSO-d<sub>6</sub>) δ ppm: 0.92 - 1.06 (m, 6 H) 1.10 - 1.48 (m, 13 H) 1.90 (quin, J=7.18 Hz, 4 H) 2.27 (s, 5 H) 2.70 - 2.79 (m, 5 H) 3.22 (d, J=7.70 Hz, 3 H) 3.34 - 3.42 (m, 4 H) 3.77 (s, 5 H) 3.88 - 3.99 (m, 3 H) 4.27 (d, J=5.26 Hz, 1 H) 4.33 (d, J=2.32 Hz, 1 H) 4.37 - 4.46 (m, 1 H) 4.65 (t, J=6.97 Hz, 2 H) 4.80 - 4.94 (m, 1 H) 5.24 (q, J=6.77 Hz, 1 H) 6.10 (d, J=2.45 Hz, 1 H) 6.15 (d, J=2.57 Hz, 1 H) 6.40 - 6.49 (m, 1 H) 6.76 - 6.84 (m, 1 H) 7.04 - 7.16 (m, 3 H) 7.45 (d, J=10.15 Hz, 1 H) 7.53 - 7.59 (m, 1 H) 7.59 - 7.66 (m, 1 H) 9.60 - 9.65 (m, 1 H)

25

**STEP 3 : Preparation of ethyl 3-[1-(4-bromobutyl)-4-methyl-1*H*-benzotriazol-5-yl]-3-{3-[(1*R*)-1-(6-hydroxy-8-methoxy-2,2-dioxo-2*H*-1,2λ<sup>6</sup>,3-benzoxathiazin-3(4*H*)-yl)ethyl]-4-methylphenyl}propanoate**

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Using General Procedure 9 starting from ethyl 3-[1-(4-hydroxybutyl)-4-methyl-1*H*-benzotriazol-5-yl]-3-{3-[(1*R*)-1-(6-hydroxy-8-methoxy-2,2-dioxo-2*H*-1,2λ<sup>6</sup>,3-benzoxathiazin-3(4*H*)-yl)ethyl]-4-methylphenyl}propanoate (1 eq.) as a reactant, the title compound (65% yield) was obtained.

5 <sup>1</sup>H-NMR (400 MHz, DMSO-d<sub>6</sub>) δ ppm: 1.00 (q, J=6.89 Hz, 5 H) 1.35 - 1.46 (m, 3 H) 1.77 (quin, J=7.03 Hz, 3 H) 1.94 - 2.05 (m, 5 H) 2.27 (s, 4 H) 2.76 (s, 4 H) 3.22 (d, J=7.70 Hz, 3 H) 3.53 (t, J=6.66 Hz, 3 H) 3.76 (s, 4 H) 3.94 (qd, J=7.09, 2.32 Hz, 3 H) 4.23 - 4.37 (m, 2 H) 4.69 (t, J=6.79 Hz, 3 H) 4.81 - 4.94 (m, 2 H) 5.24 (d, J=6.72 Hz, 1 H) 6.03 - 6.18 (m, 2 H) 6.34 - 6.51 (m, 2 H) 6.96 - 7.22 (m, 3 H) 7.44 (d, J=11.37 Hz, 1 H) 7.52 - 7.68 (m, 3 H) 9.63 (d, J=5.14 Hz,  
10 1 H)

**STEP 4: Preparation of ethyl [(2*R*)-24-methoxy-2,4,31-trimethyl-27,27-dioxo-21,26-dioxa-27λ<sup>6</sup>-thia-1,14,15,16-**

**tetraazahexacyclo[20.5.3.1<sup>3,7</sup>.1<sup>9,13</sup>.0<sup>12,16</sup>.0<sup>25,29</sup>]dotriaconta-**  
15 **3(32),4,6,9(31),10,12,14,22,24,29-decaen-8-yl]acetate**

Using General Procedure 11 starting from ethyl 3-[1-(4-bromobutyl)-4-methyl-1*H*-benzotriazol-5-yl]-3-{3-[(1*R*)-1-(6-hydroxy-8-methoxy-2,2-dioxo-2*H*-1,2λ<sup>6</sup>,3-benzoxathiazin-3(4*H*)-yl)ethyl]-4-methylphenyl}propanoate (1 eq.) as a reactant, the title compound (white  
20 solid, 69% yield) was obtained.

<sup>1</sup>H-NMR (400 MHz, DMSO-d<sub>6</sub>) δ ppm: 0.92 - 1.06 (m, 11 H) 1.11 (d, J=6.85 Hz, 4 H) 1.27 (d, J=6.85 Hz, 8 H) 1.54 - 1.92 (m, 8 H) 2.00 - 2.22 (m, 7 H) 2.23 - 2.36 (m, 13 H) 2.66 (s, 7 H) 2.81 (s, 4 H) 2.92 - 3.15 (m, 5 H) 3.33 - 3.50 (m, 7 H) 3.59 - 3.79 (m, 14 H) 3.83 - 4.00 (m, 10 H) 4.64 - 4.99 (m, 11 H) 5.15 - 5.31 (m, 5 H) 5.37 (br. s., 1 H) 6.46 (dd, J=19.93, 2.45 Hz, 3 H)  
25 6.73 (s, 1 H) 7.08 - 7.25 (m, 4 H) 7.30 (d, J=8.07 Hz, 1 H) 7.44 (d, J=7.70 Hz, 3 H) 7.68 (d, J=8.68 Hz, 1 H) 7.75 (d, J=8.80 Hz, 1 H) 7.89 (d, J=8.80 Hz, 1 H)

**STEP 5: Preparation of EXAMPLE 23**



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Using General Procedure 12 starting from ethyl [(2*R*)-24-methoxy-2,4,31-trimethyl-27,27-dioxo-21,26-dioxo-27 $\lambda^6$ -thia-1,14,15,16-tetraazahexacyclo[20.5.3.1<sup>3,7</sup>.1<sup>9,13</sup>.0<sup>12,16</sup>.0<sup>25,29</sup>]dotriaconta-3(32),4,6,9(31),10,12,14,22,24,29-decaen-8-yl]acetate (1 eq.) as a reactant, the title compound (72% yield) was obtained.

5 The enantiopure products were obtained by chromatographic separation on chiral column.

#### **Example 23a (2*R*,8*R*)**

**HRMS** calculated for C<sub>31</sub>H<sub>34</sub>N<sub>4</sub>O<sub>7</sub>S: 606.2148; [M+H]<sup>+</sup> found: 607.2223 ( $\delta$ =0.3 ppm)

**<sup>1</sup>H-NMR** (400 MHz, DMSO-d<sub>6</sub>)  $\delta$  ppm: 12 (sl, 1 H), 7.69 (d, 1 H), 7.44 (dd, 1 H), 7.39 (d, 1 H), 7.09 (d, 1 H), 6.72 (d, 1 H), 6.42 (d, 1 H), 5.38 (dl, 1 H), 5.21 (q, 1 H), 4.89 (t, 1 H), 4.76 (m, 2 H), 4.02/3.4 (2\*d, 2 H), 3.7 (m, 2 H), 3.7 (s, 3 H), 3.28/2.87 (dd, 2 H), 2.81 (s, 3 H), 2.31 (s, 3 H), 2.2/2 (m, 2 H), 1.61/1.28 (m, 2 H), 1.11 (d, 3 H)

#### **Example 23b (2*R*,8*S*)**

15 **HRMS** calculated for C<sub>31</sub>H<sub>34</sub>N<sub>4</sub>O<sub>7</sub>S: 606.2148; [M+H]<sup>+</sup> found: 607.2224 ( $\delta$ =0.5 ppm)

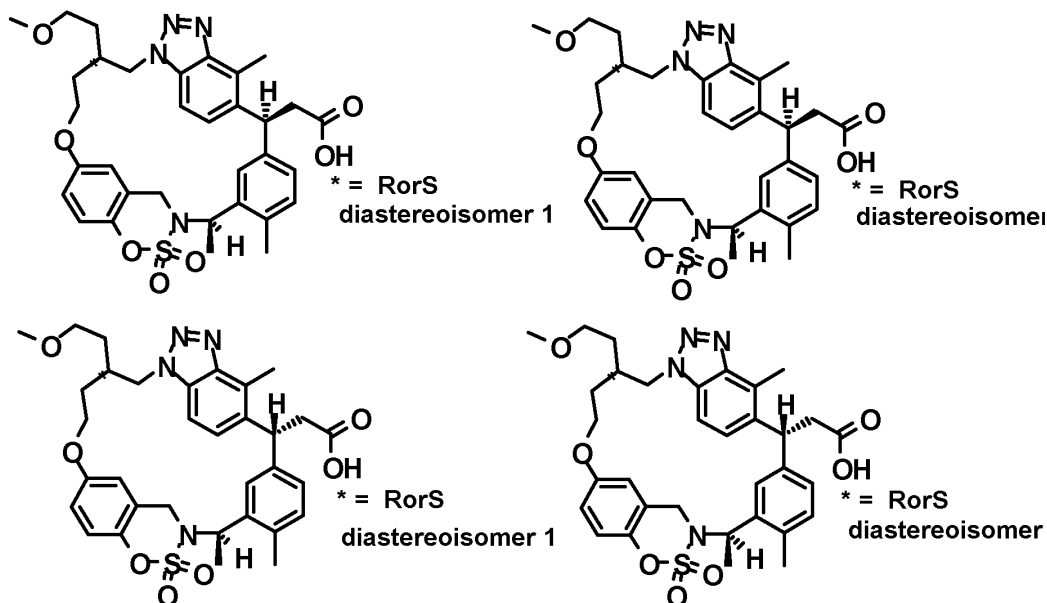
**<sup>1</sup>H-NMR** (400 MHz, DMSO-d<sub>6</sub>)  $\delta$  ppm: 12.2 (sl, 1 H), 7.88/7.74 (d, 2 H), 7.44 (dd, 1 H), 7.2 (d, 1 H), 7.11 (d, 1 H), 6.49 (d, 1 H), 5.23 (q, 1 H), 5.19 (d, 1 H), 4.8-4.67 (m, 1 H), 4.8-4.67 (m, 2 H), 3.99/3.36 (d, 2 H), 3.73 (s, 3 H), 3.63/3.41 (m, 2 H), 3.28/2.96 (dd, 2 H), 2.64 (s, 3 H), 2.29 (s, 3 H), 2.18/2.09 (m, 2 H), 1.87/1.74 (m, 2 H), 1.27 (d, 3 H)

20

**EXAMPLE 24** : [(2*R*,8*S*)-18-(2-Methoxyethyl)-2,4,31-trimethyl-27,27-dioxo-21,26-dioxo-27 $\lambda^6$ -thia-1,14,15,16-tetraazahexacyclo[20.5.3.1<sup>3,7</sup>.1<sup>9,13</sup>.0<sup>12,16</sup>.0<sup>25,29</sup>]dotriaconta-3(32),4,6,9(31),10,12,14,22,24,29-decaen-8-yl]acetic acid and [(2*R*,8*R*)-18-(2-methoxyethyl)-2,4,31-trimethyl-27,27-dioxo-21,26-dioxo-27 $\lambda^6$ -thia-1,14,15,16-tetraazahexacyclo[20.5.3.1<sup>3,7</sup>.1<sup>9,13</sup>.0<sup>12,16</sup>.0<sup>25,29</sup>]dotriaconta-3(32),4,6,9(31),10,12,14,22,24,29-decaen-8-yl]acetic acid

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#### STEP A1 : Preparation of 2-[2-(benzyloxy)ethyl]-4-methoxybutanenitrile

To a solution of 4-methoxybutanenitrile (6.88 g, 69.4 mmol) in abs. THF (1 mL/mmol, 70 mL) lithium trimethyl-*N*-(trimethylsilyl)silanaminide (1.2 eq., 1 M in THF, 83.3 mL, 83.3 mmol) was added dropwise at -78°C while continuous stirring. [(2-iodoethoxy)methyl]benzene (1.2 eq., 21.8 g, 83.3 mmol) dissolved in 35 mL of THF was added dropwise at -78°C. The reaction mixture was allowed to warm to RT and was stirred overnight. After completion of the reaction the mixture was quenched with water. 200 mL of EtOAc was added and the layers were separated. The organic layer was washed with 150 mL of brine and dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>. Filtration and concentration to dryness afforded a crude product, which was purified by normal phase silica gel chromatography using heptane-EtOAc (100:0 to 70:30) as an eluent to give the title compound (8.1 g, 50% yield).

**<sup>1</sup>H-NMR** (400 MHz, DMSO-d<sub>6</sub>) δ ppm: 7.4-7.25 (m, 5 H), 4.5 (s, 2 H), 3.55 (m, 2 H), 3.45 (m, 2 H), 3.25 (s, 3 H), 2.95 (m, 1 H), 1.9-1.7 (m, 4 H)

#### STEP A2 : Preparation of 2-[2-(benzyloxy)ethyl]-4-methoxybutan-1-amine

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Lithium aluminium hydride (1 eq., 1.3 g, 35 mmol) was placed into a round bottom flask. After addition of abs. THF (70 ml) the mixture was cooled to 10 °C. A solution of 2-[2-(benzyloxy)ethyl]-4-methoxybutanenitrile (8.1 g, 35 mmol) in abs. THF (70 mL) was added dropwise at 10°C while continuous stirring over a period of 15 min. The reaction mixture was allowed to warm to RT and stirred for further 3 h at this temperature. After completion of the reaction the mixture was cooled to 10°C and quenched with aq. Na<sub>2</sub>SO<sub>4</sub>. The mixture was stirred overnight at RT and filtered. The filter cake was washed with THF. The mother liquor was concentrated to dryness to give the title compound (8.3 g, 96% yield).

<sup>1</sup>H-NMR (400 MHz, DMSO-d<sub>6</sub>) δ ppm: 7.39-7.22 (m, 5 H), 4.44 (s, 2 H), 3.45 (t, 2 H), 3.32 (t, 2 H), 3.19 (s, 3 H), 2.46 (d, 2 H), 1.68-1.37 (m, 5 H), 1.44-1.14 (m, 2 H)

**STEP A3 : Preparation of *N*-{2-[2-(benzyloxy)ethyl]-4-methoxybutyl}-3-methyl-2-nitroaniline**

Using General Procedure 2 STEP 1 starting from 1-fluoro-3-methyl-2-nitro-benzene (1 eq.) and 2-[2-(benzyloxy)ethyl]-4-methoxybutan-1-amine (1.2 eq) as reactants, the title compound (50% yield) was obtained.

<sup>1</sup>H-NMR (400 MHz, DMSO-d<sub>6</sub>) δ ppm: 7.3 (m, 5 H), 7.2 (t, 1 H), 6.75 (d, 1 H), 6.5 (d+t, 2 H), 4.45 (s, 2 H), 3.5 (m, 2 H), 3.4 (m, 2 H), 3.2 (s, 3 H), 3.15 (m, 2 H), 2.3 (s, 3 H), 1.9 (sept., 1 H), 1.55 (m, 4 H)

**STEP A4 : Preparation of *N*-{2-[2-(benzyloxy)ethyl]-4-methoxybutyl}-4-bromo-3-methyl-2-nitroaniline**

Using General Procedure 2 STEP 2 starting from *N*-{2-[2-(benzyloxy)ethyl]-4-methoxybutyl}-3-methyl-2-nitroaniline (1 eq.) as a reactant, the title compound (62% yield) was obtained.

<sup>1</sup>H-NMR (400 MHz, DMSO-d<sub>6</sub>) δ ppm: 7.42 (d, 1 H), 7.31 (t, 2 H), 7.28 (d+t, 3 H), 6.7 (d, 1 H), 6.2 (t), 4.43 (s, 2 H), 3.5 (m, 2 H), 3.35 (m, 2 H), 3.2 (s, 3 H), 3.1 (m, 2 H), 2.25 (s, 3 H), 1.88 (m, 1 H), 1.64-1.42 (m, 4 H)

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**STEP A5 : Preparation of  $N^1$ -{2-[2-(benzyloxy)ethyl]-4-methoxybutyl}-4-bromo-3-methylbenzene-1,2-diamine**

Using General Procedure 2 STEP 3 starting from  $N$ -{2-[2-(benzyloxy)ethyl]-4-methoxybutyl}-4-bromo-3-methyl-2-nitroaniline (1 eq.) as a reactant, the title compound (quant.) was obtained.  
 **$^1\text{H-NMR}$**  (400 MHz, DMSO- $d_6$ )  $\delta$  ppm: 7.3 (m, 5 H), 6.69 (d, 1 H), 6.25 (d, 1 H), 4.68 (m, 3 H), 4.45 (s, 2 H), 3.5 (m, 2 H), 3.4 (m, 2 H), 3.2 (s, 3 H), 2.98 (d, 2 H), 2.19 (s, 3 H), 1.9 (m, 1 H), 1.75-1.5 (m, 4 H)

**STEP A6 : Preparation of 1-{2-[2-(benzyloxy)ethyl]-4-methoxybutyl}-5-bromo-4-methyl-1*H*-benzotriazole**

Using General Procedure 2 STEP 4 starting from  $N^1$ -{2-[2-(benzyloxy)ethyl]-4-methoxybutyl}-4-bromo-3-methylbenzene-1,2-diamine (1 eq.) as a reactant, the title compound (78% yield) was obtained.  
 **$^1\text{H-NMR}$**  (400 MHz, DMSO- $d_6$ )  $\delta$  ppm: 7.69 (d, 1 H), 7.6 (d, 1 H), 7.35-7.2 (m, 5 H), 4.68 (d, 2 H), 4.39 (m, 2 H), 3.48 (m, 2 H), 3.35 (m, 2 H), 3.18 (s, 3 H), 2.71 (s, 3 H), 2.3 (m, 1 H), 1.6-1.4 (m, 4 H)

**STEP A7 : Preparation of ethyl (2*E*)-3-(1-{2-[2-(benzyloxy)ethyl]-4-methoxybutyl}-4-methyl-1*H*-benzotriazol-5-yl)prop-2-enoate**

Using General Procedure 2 STEP 5 starting from 1-{2-[2-(benzyloxy)ethyl]-4-methoxybutyl}-5-bromo-4-methyl-1*H*-benzotriazole (1 eq.) as a reactant, the title compound (34% yield) was obtained.  
 **$^1\text{H-NMR}$**  (400 MHz, DMSO- $d_6$ )  $\delta$  ppm: 8.02 (d, 1 H), 7.95 (d, 1 H), 7.65 (d, 1 H), 7.35-7.2 (m, 5 H), 6.65 (d, 1 H), 4.68 (d, 2 H), 4.4 (s, 2 H), 4.22 (q, 2 H), 3.49 (m, 2 H), 3.35 (m, 2 H), 3.19 (s, 3 H), 2.8 (s, 3 H), 2.3 (m, 1 H), 1.6-1.4 (m, 4 H), 1.3 (t, 3 H)

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**STEP 1 : Preparation of ethyl 3-(1-{2-[2-(benzyloxy)ethyl]-4-methoxybutyl}-4-methyl-1*H*-benzotriazol-5-yl)-3-{3-[(1*S*)-1-hydroxyethyl]-4-methylphenyl}propanoate**

Using General Procedure 6 starting from ethyl (2*E*)-3-(1-{2-[2-(benzyloxy)ethyl]-4-methoxybutyl}-4-methyl-1*H*-benzotriazol-5-yl)prop-2-enoate (1 eq.) and (1*S*)-1-[2-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]ethan-1-ol (1.2 eq.) as reactants, the title compound (83% yield) was obtained.

**<sup>1</sup>H-NMR** (400 MHz, DMSO-*d*<sub>6</sub>) δ ppm: 7.5 (d, 1 H), 7.45 (2d, 1 H), 7.4 (d, 1 H), 7.32-7.2 (m, 5 H), 7.05 (2dd, 1 H), 6.98 (2d, 1 H), 4.99 (2d, 1 H), 4.81 (m, 2 H), 4.6 (d, 2 H), 4.4 (s, 2 H), 3.92 (q, 2 H), 3.48 (2t, 2 H), 3.3 (m, 2 H), 3.12 (s, 3 H), 3.1 (m, 2 H), 2.78 (s, 3 H), 2.28 (m, 1 H), 2.19 (s, 3 H), 1.6-1.4 (m, 4 H), 1.22 (2d, 3 H), 1 (t, 3 H)

**STEP 2 : Preparation of ethyl 3-(3-{(1*R*)-1-[6-(benzyloxy)-2,2-dioxo-2*H*-1,2λ<sup>6</sup>,3-benzoxathiazin-3(4*H*)-yl]ethyl}-4-methylphenyl)-3-(1-{2-[2-(benzyloxy)ethyl]-4-methoxybutyl}-4-methyl-1*H*-benzotriazol-5-yl)propanoate**

Using General Procedure 7 starting from ethyl 3-(1-{2-[2-(benzyloxy)ethyl]-4-methoxybutyl}-4-methyl-1*H*-benzotriazol-5-yl)-3-{3-[(1*S*)-1-hydroxyethyl]-4-methylphenyl}propanoate (1 eq.) and 6-(benzyloxy)-8-methoxy-3,4-dihydro-2*H*-1,2λ<sup>6</sup>,3-benzoxathiazine-2,2-dione (1.1 eq.) as reactants, the title compound (59% yield) was obtained.

**<sup>1</sup>H-NMR** (400 MHz, DMSO-*d*<sub>6</sub>) δ ppm: 7.6-7.2 (m, 15 H), 7.12-6.95 (m, 2 H), 6.9/6.85 (2d, 1 H), 5.28 (m, 1 H), 5.1 (2s, 2 H), 4.9 (m, 1 H), 4.6 (d, 2 H), 4.45-4.3 (m, 4 H), 3.9 (q, 2 H), 3.45 (m, 2 H), 3.3/3.2 (2m, 5 H), 3.1 (m, 2 H), 2.8/2.3 (s, 6 H), 2.28 (m, 1 H), 1.5 (m, 4 H), 1.4 (d, 3 H), 1.22 (t, 3 H)

**STEP 3 : Preparation of ethyl 3-[3-[(1*R*)-1-(6-hydroxy-2,2-dioxo-4*H*-1,2λ<sup>6</sup>,3-benzoxathiazin-3-yl)ethyl]-4-methyl-phenyl]-3-[1-[2-(2-hydroxyethyl)-4-methoxy-butyl]-4-methyl-benzotriazol-5-yl]propanoate**

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Using General Procedure 8 starting from ethyl 3-(3-[(1*R*)-1-[6-(benzyloxy)-2,2-dioxo-2*H*-1,2λ<sup>6</sup>,3-benzoxathiazin-3(4*H*)-yl]ethyl]-4-methylphenyl)-3-(1-[2-[2-(benzyloxy)ethyl]-4-methoxybutyl]-4-methyl-1*H*-benzotriazol-5-yl)propanoate (1 eq.) as a reactant, the title compound (81% yield) was obtained.

- 5 <sup>1</sup>H-NMR (400 MHz, DMSO-d<sub>6</sub>) δ ppm: 9.6/4.35 (s+t, 2 H), 7.6 (m, 2 H), 7.5 (d, 1 H), 7.12 (m, 2 H), 6.91 (d, 1 H), 6.75 (dd, 1 H), 6.6/6.55 (2d, 1 H), 5.25 (q, 1 H), 4.9 (m, 1 H), 4.6 (d, 2 H), 4.35 (m, 2 H), 3.92 (q, 2 H), 3.45 (m, 4 H), 3.21 (d, 2 H), 3.12 (s, 3 H), 2.8 (s, 3 H), 2.3 (s, 3 H), 2.25 (m, 1 H), 1.5-1.3 (m, 4 H), 1.45 (d, 3 H), 1.2 (t, 3 H)

10 **STEP 4 : Preparation of ethyl 3-{1-[2-(2-bromoethyl)-4-methoxybutyl]-4-methyl-1*H*-benzotriazol-5-yl}-3-{3-[(1*R*)-1-(6-hydroxy-2,2-dioxo-2*H*-1,2λ<sup>6</sup>,3-benzoxathiazin-3(4*H*)-yl)ethyl]-4-methylphenyl}propanoate**

- Using General Procedure 9 starting from ethyl 3-[3-[(1*R*)-1-(6-hydroxy-2,2-dioxo-4*H*-1,2λ<sup>6</sup>,3-benzoxathiazin-3-yl)ethyl]-4-methyl-phenyl]-3-[1-[2-(2-hydroxyethyl)-4-methoxy-butyl]-4-methyl-benzotriazol-5-yl]propanoate (1 eq.) as a reactant, the title compound (39% yield) was obtained.

- 15 <sup>1</sup>H-NMR (400 MHz, DMSO-d<sub>6</sub>) δ ppm: 9.6 (s, 1 H), 7.6 (d, 1 H), 7.55 (d, 1 H), 7.45 (2d, 1 H), 7.11 (m, 2 H), 6.9 (d, 1 H), 6.71 (dd, 1 H), 6.59 (2d, 1 H), 5.28 (q, 1 H), 4.9 (m, 1 H), 4.61 (d, 2 H), 4.4-4.3 (m, 2 H), 3.92 (q, 2 H), 3.58 (m, 2 H), 3.3 (m, 2 H), 3.21 (d, 2 H), 3.15 (s, 3 H), 2.78 (s, 3 H), 2.3 (m, 1 H), 2.28 (s, 3 H), 1.9-1.7 (2m, 2 H), 1.5 (m, 2 H), 1.4 (d, 3 H), 1 (2t, 3 H)

**STEP 5 : Preparation of EXAMPLE 24**

- 25 Using General Procedure 11 starting from ethyl 3-{1-[2-(2-bromoethyl)-4-methoxybutyl]-4-methyl-1*H*-benzotriazol-5-yl}-3-{3-[(1*R*)-1-(6-hydroxy-2,2-dioxo-2*H*-1,2λ<sup>6</sup>,3-benzoxathiazin-3(4*H*)-yl)ethyl]-4-methylphenyl}propanoate (1 eq.) as a reactant, ethyl [(2*R*)-18-(2-methoxyethyl)-2,4,31-trimethyl-27,27-dioxo-21,26-dioxo-27λ<sup>6</sup>-thia-1,14,15,16-tetraazahexacyclo[20.5.3.1<sup>3,7</sup>.1<sup>9,13</sup>.0<sup>12,16</sup>.0<sup>25,29</sup>]dotriaconta-3(32),4,6,9(31),10,12,14,22,24,29-

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decaen-8-yl]acetate (white solid, 57% yield) was obtained. The crude product was reacted using General Procedure 12 resulting the title compound (quant.).

The diastereo-pure products were obtained by chromatographic separation on chiral column.

5 **Example 24a (2R,8S dia1)**

**HRMS** calculated for  $C_{33}H_{38}N_4O_7S$ : 634.246;  $[M+H]^+$  found: 635.2534

**$^1H$ -NMR** (400 MHz, DMSO- $d_6$ )  $\delta$  ppm: 12.2 (ml, 1 H), 7.79 (d, 1 H), 7.61 (d, 1 H), 7.45 (dd, 1 H), 7.22 (d, 1 H), 7.02 (d, 1 H), 6.9 (d, 1 H), 6.7 (dd, 1 H), 5.4 (d, 1 H), 5.22 (q, 1 H), 4.79 (dd, 1 H), 4.75/4.6 (2dd, 2 H), 4.12/3.4 (2d, 2 H), 3.58 (m, 3 H), 3.3 (s, 3 H), 3.2-3 (m, 2 H), 2.9 (dd, 1 H), 2.6 (s, 3 H), 2.3 (s, 3 H), 1.9-1.7 (m, 5 H), 1.2 (d, 3 H)

**Example 24b (2R,8S dia2)**

**HRMS** calculated for  $C_{33}H_{38}N_4O_7S$ : 634.246;  $[M+H]^+$  found: 635.2534

**$^1H$ -NMR** (400 MHz, DMSO- $d_6$ )  $\delta$  ppm: 12.2 (ml, 1 H), 7.89 (d, 1 H), 7.78 (d, 1 H), 7.45 (dd, 1 H), 7.21 (d, 1 H), 7.04 (d, 1 H), 6.95 (d, 1 H), 6.75 (dd, 1 H), 5.4 (d, 1 H), 5.25 (q, 1 H), 4.79 (dd, 1 H), 4.61/4.55 (2dd, 2 H), 4.05/3.35 (2d, 2 H), 3.55 (t, 2 H), 3.45 (m, 1 H), 3.3 (m, 4 H), 3.1/2.9 (2m, 2 H), 2.6 (s, 3 H), 2.3 (s, 3 H), 1.9-1.7 (m, 5 H), 1.2 (d, 3 H)

**Example 24c (2R,8R dia1)**

20 **HRMS** calculated for  $C_{33}H_{38}N_4O_7S$ : 634.246;  $[M+H]^+$  found: 635.2536 ( $\delta=0.3$  ppm)

**$^1H$ -NMR** (400 MHz, DMSO- $d_6$ )  $\delta$  ppm: 7.6 (d, 1 H), 7.49 (dd, 1 H), 7.28 (d, 1 H), 7.2 (d, 1 H), 6.9 (d, 1 H), 6.89 (d, 1 H), 6.7 (dd, 1 H), 5.6 (d, 1 H), 5.26 (q, 1 H), 4.9 (dd, 1 H), 4.7/4.6 (2dd, 2 H), 4.1/3.55 (2d, 2 H), 3.6-3.35 (m, 4 H), 3.3 (s, 3 H), 3.2/2.88 (2m, 2 H), 2.8 (s, 3 H), 2.3 (s, 3 H), 1.8 (m, 3 H), 1.68/1.5 (2m, 2 H), 1.2 (d, 3 H)

25

**Example 24d (2R,8R dia2)**

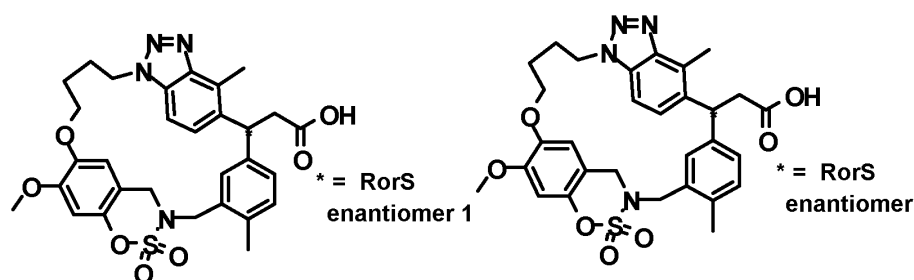
**HRMS** calculated for  $C_{33}H_{38}N_4O_7S$ : 634.246;  $[M+H]^+$  found: 635.2535 ( $\delta=0.2$  ppm)

**$^1H$ -NMR** (400 MHz, DMSO- $d_6$ )  $\delta$  ppm: 7.7 (d, 1 H), 7.49 (dd, 1 H), 7.31 (d, 1 H), 7.09 (d, 1 H), 6.91 (d, 1 H), 6.82 (d, 1 H), 6.7 (dd, 1 H), 5.65 (d, 1 H), 5.26 (q, 1 H), 4.95 (t, 1 H), 4.6 (m,

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2 H), 4.05/3.6 (2d, 2 H), 3.6-3.35 (m, 4 H), 3.23 (s, 3 H), 3.15/2.82 (2m, 2 H), 2.8 (s, 3 H), 2.32 (s, 3 H), 1.88/1.78 (2m, 2 H), 1.7 (m, 3 H), 1.1 (d, 3 H)

**EXAMPLE 25** : [23-Methoxy-4,31-dimethyl-27,27-dioxo-21,26-dioxa-27 $\lambda^6$ -thia-  
5 1,14,15,16-tetraazahexacyclo[20.5.3.1<sup>3,7</sup>.1<sup>9,13</sup>.0<sup>12,16</sup>.0<sup>25,29</sup>]dotriaconta-  
3(32),4,6,9(31),10,12,14,22,24,29-decaen-8-yl]acetic acid



#### 10 STEP C1 : Preparation of 5-(benzyloxy)-2-hydroxy-4-methoxybenzaldehyde

Using General Procedure 4 STEP 1 starting from 4-(benzyloxy)-3-methoxyphenol (1 eq.) as a reactant, the title compound (55% yield) was obtained.

**<sup>1</sup>H-NMR** (500 MHz, DMSO-d<sub>6</sub>)  $\delta$  ppm: 10.71 (s, 1 H), 10.02 (s, 1 H), 7.46-7.29 (m, 5 H),  
15 7.24 (s, 1 H), 6.58 (s, 1 H), 5.03 (s, 2 H), 3.84 (s, 3 H)

#### STEP C2 : Preparation of 6-(benzyloxy)-7-methoxy-2*H*-1,2 $\lambda^6$ ,3-benzoxathiazine-2,2-dione

Using General Procedure 4 STEP 2 starting from 5-(benzyloxy)-2-hydroxy-4-methoxy-  
20 benzaldehyde (1 eq.) as a reactant, the title compound (67% yield) was obtained.

**<sup>1</sup>H-NMR** (500 MHz, DMSO-d<sub>6</sub>)  $\delta$  ppm: 8.96 (s, 1 H), 7.64 (s, 1 H), 7.5-7.33 (m, 5 H), 7.26 (s, 1 H), 5.14 (s, 2 H), 3.95 (s, 3 H)



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**STEP C3 : Preparation of 6-(benzyloxy)-7-methoxy-3,4-dihydro-2H-1,2λ<sup>6</sup>,3-benzoxathiazine-2,2-dione**

Using General Procedure 4 STEP 3 starting from 6-(benzyloxy)-7-methoxy-2H-1,2λ<sup>6</sup>,3-benzoxathiazine-2,2-dione (1 eq.) as a reactant, the title compound (white solid, 98% yield) was obtained.

<sup>1</sup>H-NMR (500 MHz, DMSO-d<sub>6</sub>) δ ppm: 8.4 (t, 1 H), 7.52-7.29 (m, 5 H), 6.98 (s, 1 H), 6.76 (s, 1 H), 5.04 (s, 2 H), 4.42 (d, 2 H), 3.76 (s, 3 H)

**STEP 1 : Preparation of ethyl 3-(3-{[6-(benzyloxy)-7-methoxy-2,2-dioxo-2H-1,2λ<sup>6</sup>,3-benzoxathiazin-3(4H)-yl]methyl}-4-methylphenyl)-3-(1-{4-[(4-methoxyphenyl)methoxy]butyl}-4-methyl-1H-benzotriazol-5-yl)propanoate**

Using General Procedure 7 starting from ethyl 3-[3-(hydroxymethyl)-4-methylphenyl]-3-(1-{4-[(4-methoxyphenyl)methoxy]butyl}-4-methyl-1H-benzotriazol-5-yl)propanoate (1 eq.) and 6-(benzyloxy)-7-methoxy-3,4-dihydro-2H-1,2λ<sup>6</sup>,3-benzoxathiazine-2,2-dione (1.2 eq.) as reactants, the title compound (white solid, 74% yield) was obtained.

<sup>1</sup>H-NMR (500 MHz, DMSO-d<sub>6</sub>) δ ppm: 7.57 (d, 1 H), 7.48 (d, 1 H), 7.48-7.31 (m, 5 H), 7.22 (d, 1 H), 7.19 (dd, 1 H), 7.18 (m, 2 H), 7.13 (d, 1 H), 6.99 (s, 1 H), 6.88 (s, 1 H), 6.86 (m, 2 H), 5.03 (s, 2 H), 4.85 (t, 1 H), 4.62 (t, 2 H), 4.38/4.34 (d+d, 2 H), 4.29 (s, 2 H), 4.22/4.18 (d+d, 2 H), 3.91 (q, 2 H), 3.8 (s, 3 H), 3.72 (s, 3 H), 3.35 (t, 2 H), 3.19/3.16 (dd+dd, 2 H), 2.76 (s, 3 H), 2.2 (s, 3 H), 1.89 (m, 2 H), 1.44 (m, 2 H), 0.97 (t, 3 H)

**STEP 2 : Preparation of ethyl 3-[1-(4-hydroxybutyl)-4-methyl-1H-benzotriazol-5-yl]-3-{3-[(6-hydroxy-7-methoxy-2,2-dioxo-2H-1,2λ<sup>6</sup>,3-benzoxathiazin-3(4H)-yl)methyl]-4-methylphenyl}propanoate**

Using General Procedure 8 starting from ethyl 3-(3-{[6-(benzyloxy)-7-methoxy-2,2-dioxo-2H-1,2λ<sup>6</sup>,3-benzoxathiazin-3(4H)-yl]methyl}-4-methylphenyl)-3-(1-{4-[(4-methoxyphenyl)

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methoxy]butyl}-4-methyl-1*H*-benzotriazol-5-yl)propanoate (1 eq.) as a reactant, the title compound (quant.) was obtained.

**<sup>1</sup>H-NMR** (500 MHz, DMSO-d<sub>6</sub>) δ ppm: 9.26 (s, 1 H), 7.61 (d, 1 H), 7.5 (d, 1 H), 7.2 (s, 1 H), 7.19 (dd, 1 H), 7.13 (d, 1 H), 6.8 (s, 1 H), 6.6 (s, 1 H), 4.83 (t, 1 H), 4.65 (t, 2 H), 4.63 (t, 1 H),  
5 4.3 (s, 2 H), 4.19/4.16 (d+d, 2 H), 3.93 (q, 2 H), 3.79 (s, 3 H), 3.37 (m, 2 H), 3.18/3.14 (dd+dd, 2 H), 2.75 (s, 3 H), 2.21 (s, 3 H), 1.9 (m, 2 H), 1.35 (m, 2 H), 1 (t, 3 H)

**STEP 3 : Preparation of ethyl 3-[1-(4-chlorobutyl)-4-methyl-1*H*-benzotriazol-5-yl]-3-{3-[(6-hydroxy-7-methoxy-2,2-dioxo-2*H*-1,2λ<sup>6</sup>,3-benzoxathiazin-3(4*H*)-  
10 yl)methyl]-4-methylphenyl}propanoate hydrochloride**

Using General Procedure 10 starting from ethyl 3-[1-(4-hydroxybutyl)-4-methyl-1*H*-benzotriazol-5-yl]-3-{3-[(6-hydroxy-7-methoxy-2,2-dioxo-2*H*-1,2λ<sup>6</sup>,3-benzoxathiazin-3(4*H*)-  
15 yl)methyl]-4-methylphenyl}propanoate (1 eq.) as a reactant, the title compound (quant.) was obtained.

**<sup>1</sup>H-NMR** (500 MHz, DMSO-d<sub>6</sub>) δ ppm: 9.26 (s, 1 H), 7.63 (d, 1 H), 7.52 (d, 1 H), 7.2 (m, 1 H), 7.2 (m, 1 H), 7.13 (d, 1 H), 6.8 (s, 1 H), 6.59 (s, 1 H), 4.83 (t, 1 H), 4.69 (t, 2 H), 4.3 (s, 2 H), 4.19/4.15 (d+d, 2 H), 3.93 (q, 2 H), 3.79 (s, 3 H), 3.64 (t, 2 H), 3.19/3.15 (dd+dd, 2 H), 2.75 (s, 3 H), 2.21 (s, 3 H), 1.99 (m, 2 H), 1.68 (m, 2 H), 0.99 (t, 3 H)

20

**STEP 4 : Preparation of ethyl [23-methoxy-4,31-dimethyl-27,27-dioxo-21,26-dioxa-27λ<sup>6</sup>-thia-1,14,15,16-tetraazahexacyclo[20.5.3.1<sup>3,7</sup>.1<sup>9,13</sup>.0<sup>12,16</sup>.0<sup>25,29</sup>]dotriaconta-3(32),4,6,9(31),10,12,14,22,24,29-decaen-8-yl]acetate**

25 Using General Procedure 11 starting from ethyl 3-[1-(4-chlorobutyl)-4-methyl-1*H*-benzotriazol-5-yl]-3-{3-[(6-hydroxy-7-methoxy-2,2-dioxo-2*H*-1,2λ<sup>6</sup>,3-benzoxathiazin-3(4*H*)-yl)methyl]-4-methylphenyl}propanoate hydrochloride (1 eq.) as a reactant, the title compound (white solid, 34% yield) was obtained.

**<sup>1</sup>H-NMR** (500 MHz, DMSO-d<sub>6</sub>) δ ppm: 7.69 (d, 1 H), 7.47 (dd, 1 H), 7.46 (d, 1 H), 7.28 (d, 1  
30 H), 6.75 (s, 1 H), 6.56 (d, 1 H), 5.77 (s, 1 H), 4.82/4.75 (m+m, 2 H), 4.78 (dd, 1 H), 4.18/3.87

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(d+d, 2 H), 3.93 (q, 2 H), 3.93/3.69 (d+d, 2 H), 3.72 (s, 3 H), 3.56/3.3 (m+m, 2 H), 3.14/3.06 (dd+dd, 2 H), 2.61 (s, 3 H), 2.32 (s, 3 H), 2.2/2.02 (m+m, 2 H), 1.78/1.61 (m+m, 2 H), 1.01 (t, 3 H)

## 5 STEP 5 : Preparation of EXAMPLE 25

Using General Procedure 12 starting from ethyl [23-methoxy-4,31-dimethyl-27,27-dioxo-21,26-dioxa-27 $\lambda^6$ -thia-1,14,15,16-tetraazahexacyclo[20.5.3.1<sup>3,7</sup>.1<sup>9,13</sup>.0<sup>12,16</sup>.0<sup>25,29</sup>]dotriaconta-3(32),4,6,9(31),10,12,14,22,24,29-decaen-8-yl]acetate (1 eq.) as a reactant, the title compound  
10 (white solid, 86% yield) was obtained.

The enantiopure products were obtained by chromatographic separation on chiral column.

### Example 25a (E1, optical purity: 99.9%)

HRMS calculated for C<sub>30</sub>H<sub>32</sub>N<sub>4</sub>O<sub>7</sub>S: 592.1992; [M+H]<sup>+</sup> found: 593.2048 ( $\delta$  = -2.8 ppm)

15

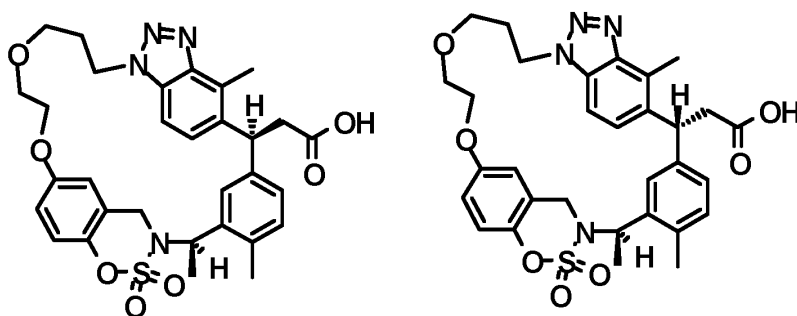
### Example 25b (E2, optical purity~99.4%)

HRMS calculated for C<sub>30</sub>H<sub>32</sub>N<sub>4</sub>O<sub>7</sub>S: 592.1992; [M+H]<sup>+</sup> found: 593.2047 ( $\delta$  = -2.9 ppm)

<sup>1</sup>H-NMR (500 MHz, DMSO-d<sub>6</sub>)  $\delta$  ppm: 12.54 (br., 1 H), 7.68 (d, 1 H), 7.48 (brd., 1 H), 7.45 (d, 1 H), 7.27 (d, 1 H), 6.74 (s, 1 H), 6.53 (brs., 1 H), 5.75 (s, 1 H), 4.81/4.74 (m+m, 2 H), 4.75  
20 (m, 1 H), 4.16/3.87 (d+d, 2 H), 3.93/3.69 (d+d, 2 H), 3.72 (s, 3 H), 3.55/3.28 (m+m, 2 H), 2.99/2.92 (dd+dd, 2 H), 2.6 (s, 3 H), 2.32 (s, 3 H), 2.2/2.03 (m+m, 2 H), 1.78/1.61 (m+m, 2 H)  
<sup>13</sup>C-NMR (125 MHz, DMSO-d<sub>6</sub>)  $\delta$  ppm: 173.3, 131.3, 131.3, 128.8, 127.3, 110.8, 107.9, 102.9, 68.3, 56.3, 51.9, 48.4, 48.2, 42, 41.3, 27, 25.6, 18.5, 13.4

25 **EXAMPLE 26** : [(2*R*,8*S*)-2,4,33-Trimethyl-29,29-dioxo-20,23,28-trioxa-29 $\lambda^6$ -thia-1,14,15,16-tetraazahexacyclo[22.5.3.1<sup>3,7</sup>.1<sup>9,13</sup>.0<sup>12,16</sup>.0<sup>27,31</sup>]tetratriaconta-3(34),4,6,9(33),10,12,14,24,26,31-decaen-8-yl]acetic acid and  
[(2*R*,8*R*)-2,4,33-trimethyl-29,29-dioxo-20,23,28-trioxa-29 $\lambda^6$ -thia-1,14,15,16-tetraazahexacyclo[22.5.3.1<sup>3,7</sup>.1<sup>9,13</sup>.0<sup>12,16</sup>.0<sup>27,31</sup>]tetratriaconta-3(34),4,6,9(33),10,12,14,24,26,31-decaen-8-yl]acetic acid  
30

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#### STEP A1 : Preparation of *N*-{3-[2-(benzyloxy)ethoxy]propyl}-3-methyl-2-nitroaniline

5

Using General Procedure 2 STEP 1 starting from 1-fluoro-3-methyl-2-nitrobenzene (1 eq.) and 3-[2-(benzyloxy)ethoxy]propan-1-amine hydrochloride (1.2 eq) as a reactant, the title compound (85% yield) was obtained.

<sup>1</sup>H-NMR (400 MHz, DMSO-d<sub>6</sub>) δ ppm: 7.38-7.27 (m, 5 H), 7.24 (dd, 1 H), 6.77 (d, 1 H), 6.54 (d, 1 H), 6.48 (t, 1 H), 4.49 (s, 2 H), 3.58 (m, 4 H), 3.5 (t, 2 H), 3.23 (q, 2 H), 2.3 (s, 3 H), 1.8 (quint, 2 H)

#### STEP A2 : Preparation of *N*-{3-[2-(benzyloxy)ethoxy]propyl}-4-bromo-3-methyl-2-nitroaniline

15

Using General Procedure 2 STEP 2 starting from *N*-{3-[2-(benzyloxy)ethoxy]propyl}-3-methyl-2-nitroaniline (1 eq.) as a reactant, the title compound (99% yield) was obtained.

<sup>1</sup>H-NMR (400 MHz, DMSO-d<sub>6</sub>) δ ppm: 7.49 (d, 1 H), 7.38-7.25 (m, 5 H), 6.72 (d, 1 H), 6.18 (t, 1 H), 4.49 (s, 2 H), 3.6-3.5 (m, 4 H), 3.48 (t, 2 H), 3.2 (q, 2 H), 2.25 (s, 3 H), 1.77 (quint, 2 H)

#### STEP A3 : Preparation of *N*<sup>1</sup>-{3-[2-(benzyloxy)ethoxy]propyl}-4-bromo-3-methylbenzene-1,2-diamine

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Using General Procedure 2 STEP 3 starting from *N*-{3-[2-(benzyloxy)ethoxy]propyl}-4-bromo-3-methyl-2-nitroaniline (1 eq.) as a reactant, the title compound (quant.) was obtained.

<sup>1</sup>H-NMR (400 MHz, DMSO-d<sub>6</sub>) δ ppm: 7.37-7.24 (m, 5 H), 6.71 (d, 1 H), 6.27 (d, 1 H), 4.9-4.5 (m, 3 H), 4.49 (s, 2 H), 3.56 (m, 4 H), 3.52 (t, 2 H), 3.06 (t, 2 H), 2.16 (s, 3 H), 1.82 (m, 2 H)

**STEP A4 : Preparation of 1-{3-[2-(benzyloxy)ethoxy]propyl}-5-bromo-4-methyl-1*H*-benzotriazole**

Using General Procedure 2 STEP 4 starting from *N*<sup>1</sup>-{3-[2-(benzyloxy)ethoxy]propyl}-4-bromo-3-methylbenzene-1,2-diamine (1 eq.) as a reactant, the title compound (42% yield) was obtained.

<sup>1</sup>H-NMR (400 MHz, DMSO-d<sub>6</sub>) δ ppm: 2.13 (quint, J=6.39 Hz, 2 H) 2.71 (s, 3 H) 3.35 (t, J=6.05 Hz, 2 H) 3.41 - 3.58 (m, 6 H) 4.43 - 4.47 (m, 3 H) 4.74 (t, J=6.72 Hz, 2 H) 7.20 - 7.37 (m, 9 H) 7.55 - 7.68 (m, 3 H)

**STEP A5 : Preparation of ethyl (2*E*)-3-(1-{3-[2-(benzyloxy)ethoxy]propyl}-4-methyl-1*H*-benzotriazol-5-yl)prop-2-enoate**

Using General Procedure 2 STEP 5 starting from 1-{3-[2-(benzyloxy)ethoxy]propyl}-5-bromo-4-methyl-1*H*-benzotriazole (1 eq.) as a reactant, the title compound (98% yield) was obtained.

<sup>1</sup>H-NMR (400 MHz, DMSO-d<sub>6</sub>) δ ppm: 8.01 (d, 1 H), 7.89 (d, 1 H), 7.69 (d, 1 H), 7.38-7.25 (m+m, 5 H), 6.61 (d, 1 H), 4.74 (t, 2 H), 4.47 (s, 2 H), 4.22 (q, 2 H), 3.54-3.47 (m+m, 4 H), 3.37 (t, 2 H), 2.8 (s, 3 H), 2.23 (quint, 2 H), 1.29 (t, 3 H)

**STEP 1: Preparation of ethyl 3-(1-{3-[2-(benzyloxy)ethoxy]propyl}-4-methyl-1*H*-benzotriazol-5-yl)-3-{3-[(1*S*)-1-hydroxyethyl]-4-methylphenyl}propanoate**

Using General Procedure 6 starting from ethyl (2*E*)-3-(1-{3-[2-(benzyloxy)ethoxy]propyl}-4-methyl-1*H*-benzotriazol-5-yl)prop-2-enoate (1 eq.) and (1*S*)-1-[2-methyl-5-(4,4,5,5-

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tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]ethan-1-ol (1 eq.) as reactants, the title compound (59% yield) was obtained.

<sup>1</sup>H-NMR (400 MHz, DMSO-d<sub>6</sub>) δ ppm: 7.56 (d, 1 H), 7.41 (d, 1 H), 7.39 (m, 1 H), 7.35-7.22 (m, 5 H), 7.02 (dd, 1 H), 6.99 (d, 1 H), 4.97 (m, 1 H), 4.82 (m, 1 H), 4.82 (m, 1 H), 4.68 (t, 2 H), 4.46 (s, 2 H), 3.92 (q, 2 H), 3.52/3.49 (m, 4 H), 3.35 (t, 2 H), 3.14-3.07 (m, 2 H), 2.75 (s, 3 H), 2.19 (s, 3 H), 2.1 (quint, 2 H), 1.21 (d, 3 H), 1 (t, 3 H)

**STEP 2 : Preparation of ethyl 3-{3-[(1*R*)-1-(6-hydroxy-2,2-dioxo-2*H*-1,2λ<sup>6</sup>,3-benzoxathiazin-3(4*H*)-yl)ethyl]-4-methylphenyl}-3-{1-[3-(2-hydroxyethoxy)propyl]-4-methyl-1*H*-benzotriazol-5-yl}propanoate**

Using General Procedure 7 starting from ethyl 3-(1-{3-[2-(benzyloxy)ethoxy]propyl}-4-methyl-1*H*-benzotriazol-5-yl)-3-{3-[(1*S*)-1-hydroxyethyl]-4-methylphenyl}propanoate (1 eq.) and 6-(benzyloxy)-3,4-dihydro-2*H*-1,2λ<sup>6</sup>,3-benzoxathiazine-2,2-dione (1.1 eq.) as reactants, ethyl 3-(3-{(1*R*)-1-[6-(benzyloxy)-2,2-dioxo-2*H*-1,2λ<sup>6</sup>,3-benzoxathiazin-3(4*H*)-yl]ethyl}-4-methylphenyl)-3-(1-{3-[2-(benzyloxy)ethoxy]propyl}-4-methyl-1*H*-benzotriazol-5-yl)propanoate (orange oil, 84% yield) was obtained. The crude product was reacted using General Procedure 8 resulting the title compound (white solid, 87% yield).

<sup>1</sup>H-NMR (400 MHz, DMSO-d<sub>6</sub>) δ ppm: 9.62 (m, 1 H), 7.64-7.54 (m, 2 H), 7.47/7.47 (2sl, 1 H), 7.14-7.08 (m, 2 H), 6.92/6.9 (2d, 1 H), 6.76-6.7 (m, 1 H), 6.57 (2d, 1 H), 5.25 (m, 1 H), 4.88 (q, 1 H), 4.7 (t, 2 H), 4.57 (m, 1 H), 4.36/4.31 (s+dd, 2 H), 3.95 (2d, 2 H), 3.47 (m, 2 H), 3.39-3.28 (m, 4 H), 3.22 (m, 2 H), 2.77 (s, 3 H), 2.28 (s, 3 H), 2.1 (m, 2 H), 1.43/1.41 (2d, 3 H), 1.01/1 (2t, 3 H)

**STEP 3 : Preparation of ethyl 3-{1-[3-(2-bromoethoxy)propyl]-4-methyl-1*H*-benzotriazol-5-yl}-3-{3-[(1*R*)-1-(6-hydroxy-2,2-dioxo-2*H*-1,2λ<sup>6</sup>,3-benzoxathiazin-3(4*H*)-yl)ethyl]-4-methylphenyl}propanoate**

Using General Procedure 9 starting from ethyl 3-{3-[(1*R*)-1-(6-hydroxy-2,2-dioxo-2*H*-1,2λ<sup>6</sup>,3-benzoxathiazin-3(4*H*)-yl)ethyl]-4-methylphenyl}-3-{1-[3-(2-hydroxyethoxy)propyl]-4-

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methyl-1*H*-benzotriazol-5-yl}propanoate (1 eq.) as a reactant, the title compound (white solid, 60% yield) was obtained.

**<sup>1</sup>H-NMR** (400 MHz, DMSO-d<sub>6</sub>) δ ppm: 9.55 (s, 1 H), 7.7-7.5 (2d, 2 H), 7.49 (2d, 1 H), 7.11 (m, 2 H), 6.91 (d, 1 H), 6.71 (2dd, 1 H), 6.48 (2d, 1 H), 5.28 (m, 1 H), 4.9 (m, 1 H), 4.7 (t, 2 H),  
 5 4.4-4.3 (m, 2 H), 3.95 (q, 2 H), 3.68 (t, 2 H), 3.55 (t, 2 H), 3.41 (t, 2 H), 3.21 (d, 2 H), 2.79 (s, 3 H), 2.3 (s, 3 H), 2.12 (m, 2 H), 1.45 (2d, 3 H), 1.02 (2t, 3 H)

**STEP 4 : Preparation of ethyl [(2*R*)-2,4,33-trimethyl-29,29-dioxo-20,23,28-trioxa-29λ<sup>6</sup>-thia-1,14,15,16-tetraazahexacyclo[22.5.3.1<sup>3,7</sup>.1<sup>9,13</sup>.0<sup>12,16</sup>.0<sup>27,31</sup>]tetratriaconta-3(34),4,6,9(33),10,12,14,24,26,31-decaen-8-yl]acetate**  
 10

Using General Procedure 11 starting from ethyl 3-{1-[3-(2-bromoethoxy)propyl]-4-methyl-1*H*-benzotriazol-5-yl}-3-{3-[(1*R*)-1-(6-hydroxy-2,2-dioxo-2*H*-1,2λ<sup>6</sup>,3-benzoxathiazin-3(4*H*)-yl)ethyl]-4-methylphenyl}propanoate (1 eq.) as a reactant, the title compound (white solid, quant.)  
 15 was obtained.

**<sup>1</sup>H-NMR** (400 MHz, DMSO-d<sub>6</sub>) δ ppm: 1.01 (td, J=7.09, 4.16 Hz, 6 H) 1.18 (d, J=6.85 Hz, 2 H) 1.55 (d, J=6.85 Hz, 3 H) 2.18 (d, J=5.38 Hz, 3 H) 2.26 - 2.36 (m, 6 H) 2.79 (s, 2 H) 2.85 (s, 3 H) 2.95 (dd, J=15.77, 8.31 Hz, 1 H) 3.14 - 3.26 (m, 3 H) 3.39 - 3.54 (m, 3 H) 3.55 - 3.61 (m, 1 H) 3.61 - 3.73 (m, 2 H) 3.74 - 3.85 (m, 2 H) 3.87 - 3.98 (m, 5 H) 4.01 (d, J=6.60 Hz, 1 H) 4.08  
 20 (t, J=4.71 Hz, 2 H) 4.19 (d, J=17.73 Hz, 1 H) 4.35 (d, J=17.61 Hz, 1 H) 4.53 - 4.82 (m, 4 H) 4.83 - 4.96 (m, 2 H) 5.23 - 5.31 (m, 1 H) 5.33 - 5.42 (m, 1 H) 6.25 (d, J=2.81 Hz, 1 H) 6.50 (d, J=2.81 Hz, 1 H) 6.78 - 6.94 (m, 2 H) 6.96 - 7.04 (m, 2 H) 7.10 (dd, J=19.38, 8.25 Hz, 2 H) 7.17 - 7.25 (m, 2 H) 7.42 (d, J=6.48 Hz, 1 H) 7.54 - 7.65 (m, 4 H)

**STEP 5 : Preparation of EXAMPLE 26**  
 25

Using General Procedure 12 starting from ethyl [(2*R*)-2,4,33-trimethyl-29,29-dioxo-20,23,28-trioxa-29λ<sup>6</sup>-thia-1,14,15,16-tetraazahexacyclo[22.5.3.1<sup>3,7</sup>.1<sup>9,13</sup>.0<sup>12,16</sup>.0<sup>27,31</sup>]tetratriaconta-3(34),4,6,9(33),10,12,14,24,26,31-decaen-8-yl]acetate (1 eq.) as a reactant, the title compound  
 30 (white solid, 85% yield) was obtained.

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The diastereo-pure products were obtained by chromatographic separation on chiral column.

**Example 26a (2R,8S)**

**HRMS** calculated for  $C_{31}H_{34}N_4O_7S$ : 606.2148;  $[M+H]^+$  found: 607.2223 ( $\delta=0.3$  ppm)

5  **$^1H$ -NMR** (400 MHz, DMSO- $d_6$ )  $\delta$  ppm: 12.1 (sl, 1 H), 7.62/7.59 (d, 2 H), 7.59 (d, 1 H), 7.19 (dd, 1 H), 7.08 (d, 1 H), 7.01 (d, 1 H), 6.91 (dd, 1 H), 6.49 (d, 1 H), 5.37 (q, 1 H), 4.87 (t, 1 H), 4.77/4.67 (m, 2 H), 4.33/3.95 (d, 2 H), 4.08 (t, 2 H), 3.79/3.66 (m, 2 H), 3.49 (m, 2 H), 3.11 (m, 2 H), 2.83 (s, 3 H), 2.29 (s, 3 H), 2.19 (m, 2 H), 1.54 (d, 3 H)

10 **Example 26b (2R,8R)**

**HRMS** calculated for  $C_{31}H_{34}N_4O_7S$ : 606.2148;  $[M+H]^+$  found: 607.2223 ( $\delta=0.3$  ppm)

**$^1H$ -NMR** (400 MHz, DMSO- $d_6$ )  $\delta$  ppm: 12.11 (sl, 1 H), 7.61 (d, 1 H), 7.43 (dd, 1 H), 7.23 (d, 1 H), 7.11 (d, 1 H), 6.99 (d, 1 H), 6.88 (d, 1 H), 6.85 (dd, 1 H), 6.24 (d, 1 H), 5.28 (q, 1 H), 4.9 (t, 1 H), 4.75/4.61 (m, 2 H), 4.16/3.96 (d, 2 H), 3.91/3.83 (m, 2 H), 3.71/3.59 (m, 2 H), 3.59/3.5 (m, 2 H), 3.11/2.84 (dd, 2 H), 2.8 (s, 3 H), 2.3 (s, 3 H), 2.29/2.18 (m, 2 H), 1.19 (d, 3 H)

**EXAMPLE 27 : [(2R,8R)-2,4,33-Trimethyl-29,29-dioxo-19,23,28-trioxa-29 $\lambda^6$ -thia-**

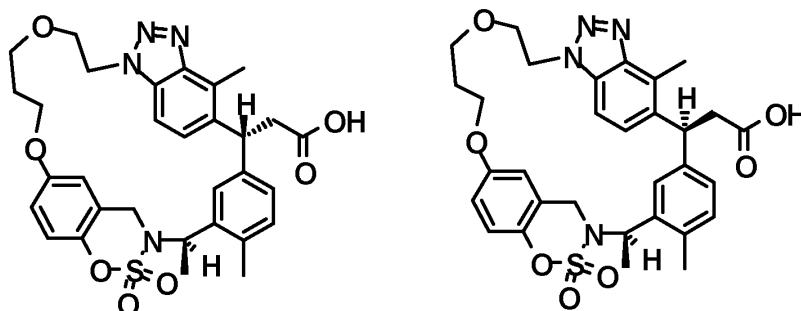
**1,14,15,16-tetraazahexacyclo[22.5.3.1<sup>3,7</sup>.1<sup>9,13</sup>.0<sup>12,16</sup>.0<sup>27,31</sup>]tetratriaconta-3(34),4,6,9(33),10,12,14,24,26,31-decaen-8-yl]acetic acid and**

20 **[(2R,8S)-2,4,33-trimethyl-29,29-dioxo-19,23,28-trioxa-29 $\lambda^6$ -thia-**

**1,14,15,16-tetraazahexacyclo[22.5.3.1<sup>3,7</sup>.1<sup>9,13</sup>.0<sup>12,16</sup>.0<sup>27,31</sup>]tetratriaconta-3(34),4,6,9(33),10,12,14,24,26,31-decaen-8-yl]acetic acid**



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#### STEP A1 : Preparation of *tert*-butyl {2-[3-(benzyloxy)propoxy]ethyl}carbamate

5 To a solution of 3-(benzyloxy)propyl 4-methylbenzene-1-sulfonate (41 g, 130 mmol) in toluene (2 mL/mmol, 260 mL) tetrabutylammonium-hydrogensulfate (0.1 eq., 4.3 g, 13 mmol), *tert*-butyl (2-hydroxyethyl)carbamate (1 eq., 21 g, 130 mmol) and 50 wt% aq. NaOH (9 eq., 92 g, 1.2 mol) were added. The mixture was heated at 85 °C for 16 h. After completion of the reaction the mixture was diluted with 1 L EtOAc. The mixture was washed with 2 L of sat. aq. NH<sub>4</sub>Cl

10 solution, the layers were separated. The organic layer was dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>, filtered, concentrated to dryness to give the crude product, which was purified by reverse-phase chromatography using water-MeCN eluent system to give the title compound (19.6 g, yellow oil, 47% yield).

<sup>1</sup>H-NMR (400 MHz, DMSO-d<sub>6</sub>) δ ppm: 7.38-7.24 (m, 5 H), 6.73 (t, 1 H), 4.44 (s, 2 H), 3.49 (t, 2 H), 3.44 (t, 2 H), 3.33 (t, 2 H), 3.04 (q, 2 H), 1.76 (quint, 2 H), 1.38 (s, 9 H)

15

#### STEP A2 : Preparation of 2-[3-(benzyloxy)propoxy]ethan-1-amine hydrochloride

To a solution of *tert*-butyl {2-[3-(benzyloxy)propoxy]ethyl}carbamate (19.6 g, 59.5 mmol) in dioxane (5 mL/mmol, 298 mL) HCl (4N in dioxane) (4 eq., 59.5 mL) was added at RT. The reaction mixture was stirred overnight at RT. After completion of the reaction the solvent was evaporated to dryness under reduced pressure. The crude product was used without further purification as an HCl salt (15.6 g, quant.).

20

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**<sup>1</sup>H-NMR** (400 MHz, DMSO-d<sub>6</sub>) δ ppm: 7.98 (s, 3 H), 7.4-7.36 (m, 5 H), 4.46 (s, 2 H), 3.56 (t, 2 H), 3.5 (t, 2 H), 3.5 (t, 2 H), 2.93 (t, 2 H), 1.81 (quint, 2 H)

**STEP A3 : Preparation of *N*-{2-[3-(benzyloxy)propoxy]ethyl}-3-methyl-2-nitroaniline**

5

Using General Procedure 2 STEP 1 starting from 1-fluoro-3-methyl-2-nitrobenzene (1 eq.) and 2-[3-(benzyloxy)propoxy]ethan-1-amine hydrochloride (1.2 eq.) as reactants, the title compound (93% yield) was obtained.

**<sup>1</sup>H-NMR** (400 MHz, DMSO-d<sub>6</sub>) δ ppm: 7.38-7.24 (m, 5 H), 7.27 (m, 1 H), 6.82 (d, 1 H), 6.59 (d, 1 H), 6.46 (t, 1 H), 4.42 (s, 2 H), 3.57 (t, 2 H), 3.52-3.47 (m, 4 H), 3.33 (dt, 2 H), 2.31 (s, 3 H), 1.79 (quint, 2 H)

10

**STEP A4 : Preparation of *N*-{2-[3-(benzyloxy)propoxy]ethyl}-4-bromo-3-methyl-2-nitroaniline**

15

Using General Procedure 2 STEP 2 starting from *N*-{2-[3-(benzyloxy)propoxy]ethyl}-3-methyl-2-nitroaniline (1 eq.) as a reactant, the title compound (58% yield) was obtained.

**<sup>1</sup>H-NMR** (400 MHz, DMSO-d<sub>6</sub>) δ ppm: 7.54 (d, 1 H), 7.38-7.23 (m, 5 H), 6.8 (d, 1 H), 6.09 (t, 1 H), 4.42 (s, 2 H), 3.51 (t, 2 H), 3.47 (m, 4 H), 3.3 (q, 2 H), 2.38 (s, 3 H), 1.77 (quint, 2 H)

20

**STEP A5 : Preparation of *N*<sup>1</sup>-{2-[3-(benzyloxy)propoxy]ethyl}-4-bromo-3-methylbenzene-1,2-diamine**

Using General Procedure 2 STEP 3 starting from *N*-{2-[3-(benzyloxy)propoxy]ethyl}-4-bromo-3-methyl-2-nitroaniline (1 eq.) as a reactant, the title compound (quant.) was obtained.

25

**<sup>1</sup>H-NMR** (400 MHz, DMSO-d<sub>6</sub>) δ ppm: 7.38-7.23 (m, 5 H), 6.71 (d, 1 H), 6.29 (d, 1 H), 4.6 (sl, 3 H), 4.42 (s, 2 H), 3.56/3.5 (m, 2 H), 3.56/3.5 (m, 4 H), 3.16 (t, 2 H), 2.17 (s, 3 H), 1.79 (quint, 2 H)

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**STEP A6 : Preparation of ethyl (2E)-3-(1-{2-[3-(benzyloxy)propoxy]ethyl}-4-methyl-1H-benzotriazol-5-yl)prop-2-enoate**

Using General Procedure 2 STEP 4 starting from *N*<sup>1</sup>-{2-[3-(benzyloxy)propoxy]ethyl}-4-bromo-3-methylbenzene-1,2-diamine (1 eq.) as a reactant, 1-{2-[3-(benzyloxy)propoxy]ethyl}-5-bromo-4-methyl-1*H*-benzotriazole (29% yield) was obtained. The crude product was reacted using General Procedure 2 STEP 5 to give the title compound (91% yield).

<sup>1</sup>H-NMR (400 MHz, DMSO-d<sub>6</sub>) δ ppm: 8.01 (d, 1 H), 7.92 (d, 1 H), 7.69 (d, 1 H), 7.3 (t, 2 H), 7.25 (t, 1 H), 7.2 (d, 2 H), 6.62 (d, 1 H), 4.85 (t, 2 H), 4.22 (s, 2 H), 4.21 (q, 2 H), 3.82 (t, 2 H), 3.4 (t, 2 H), 3.21 (t, 2 H), 2.79 (s, 3 H), 1.6 (quint, 2 H), 1.28 (t, 3 H)

**STEP 1 : Preparation of ethyl 3-(1-{2-[3-(benzyloxy)propoxy]ethyl}-4-methyl-1H-benzotriazol-5-yl)-3-{3-[(1*S*)-1-hydroxyethyl]-4-methylphenyl}propanoate**

Using General Procedure 6 starting from ethyl (2*E*)-3-(1-{2-[3-(benzyloxy)propoxy]ethyl}-4-methyl-1*H*-benzotriazol-5-yl)prop-2-enoate (1 eq.) and (1*S*)-1-[2-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]ethan-1-ol (1 eq.) as reactants, the title compound (48% yield) was obtained.

<sup>1</sup>H-NMR (400 MHz, DMSO-d<sub>6</sub>) δ ppm: 7.58 (d, 1 H), 7.44 (d, 1 H), 7.4 (d, 1 H), 7.31 (t, 2 H), 7.24 (t, 1 H), 7.21 (d, 2 H), 7.03 (dd, 1 H), 6.97 (d, 1 H), 4.83 (m, 1 H), 4.83 (m, 1 H), 4.8 (m, 2 H), 4.25 (s, 2 H), 3.97 (d, 1 H), 3.92 (q, 2 H), 3.82 (t, 2 H), 3.4 (t, 2 H), 3.25 (m, 2 H), 3.15-3.05 (m, 2 H), 2.76 (s, 3 H), 2.18 (s, 3 H), 1.61 (quint, 2 H), 1.21 (d, 3 H), 1 (t, 3 H)

**STEP 2 : Preparation of ethyl 3-{3-[(1*R*)-1-(6-hydroxy-2,2-dioxo-2*H*-1,2λ<sup>6</sup>,3-benzoxathiazin-3(4*H*)-yl)ethyl]-4-methylphenyl}-3-{1-[2-(3-hydroxypropoxy)ethyl]-4-methyl-1*H*-benzotriazol-5-yl}propanoate**

Using General Procedure 7 starting from ethyl 3-(1-{2-[3-(benzyloxy)propoxy]ethyl}-4-methyl-1*H*-benzotriazol-5-yl)-3-{3-[(1*S*)-1-hydroxyethyl]-4-methylphenyl}propanoate (1.1 eq.) and 6-(benzyloxy)-3,4-dihydro-2*H*-1,2λ<sup>6</sup>,3-benzoxathiazine-2,2-dione (1.1 eq.) as

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reactants, ethyl 3-(3-((1*R*)-1-[6-(benzyloxy)-2,2-dioxo-2*H*-1,2λ<sup>6</sup>,3-benzoxathiazin-3(4*H*)-yl]ethyl)-4-methylphenyl)-3-(1-[2-[3-(benzyloxy)propoxy]ethyl]-4-methyl-1*H*-benzotriazol-5-yl)propanoate (yellow oil, 86% yield) was obtained. The crude product was reacted using General Procedure 8 resulting the title compound (yellow oil, 83% yield).

- 5 <sup>1</sup>H-NMR (400 MHz, DMSO-d<sub>6</sub>) δ ppm: 9.62 (2m, 2 H), 7.65-7.42 (m, 2 H), 7.47/7.45 (2sl, 1 H), 7.14-7.07 (m, 2 H), 6.92/6.9 (2d, 1 H), 6.75-6.7 (m, 1 H), 6.58 (2d, 1 H), 5.25 (q, 1 H), 4.87 (q, 1 H), 4.8 (t, 2 H), 4.36/4.32 (2s, 2 H), 4.31-4.24 (m, 1 H), 3.94 (2q, 2 H), 3.82 (m, 2 H), 3.39 (2t, 2 H), 3.29 (q, 2 H), 3.22 (m, 2 H), 2.76 (s, 3 H), 2.27 (s, 3 H), 1.5 (m, 2 H), 1.43/1.41 (2d, 3 H), 1.01/1 (2t, 3 H)

10

**STEP 3 : Preparation of ethyl 3-{1-[2-(3-bromopropoxy)ethyl]-4-methyl-1*H*-benzotriazol-5-yl}-3-{3-[(1*R*)-1-(6-hydroxy-2,2-dioxo-2*H*-1,2λ<sup>6</sup>,3-benzoxathiazin-3(4*H*)-yl)ethyl]-4-methylphenyl}propanoate**

- 15 Using General Procedure 9 starting from ethyl 3-{3-[(1*R*)-1-(6-hydroxy-2,2-dioxo-2*H*-1,2λ<sup>6</sup>,3-benzoxathiazin-3(4*H*)-yl)ethyl]-4-methylphenyl}-3-{1-[2-(3-hydroxypropoxy)ethyl]-4-methyl-1*H*-benzotriazol-5-yl}propanoate (1 eq.) as a reactant, the title compound (white solid, 49% yield) was obtained.

- 20 <sup>1</sup>H-NMR (400 MHz, DMSO-d<sub>6</sub>) δ ppm: 9.55 (s, 1 H), 7.7-7.55 (2d, 2 H), 7.49 (2d, 1 H), 7.1 (m, 2 H), 6.9 (d, 1 H), 6.71 (2, 1 H), 6.6 (2d, 1 H), 5.25 (m, 1 H), 4.9 (m, 1 H), 4.81 (t, 2 H), 4.4-4.25 (m, 2 H), 3.95 (m, 2 H), 3.85 (t, 2 H), 3.41 (t, 2 H), 3.3 (t, 2 H), 3.21 (d, 2 H), 2.76 (s, 3 H), 2.3 (s, 3 H), 1.85 (m, 2 H), 1.45 (2d, 3 H), 1.02 (2t, 3 H)

- 25 **STEP 4 : Preparation of ethyl [(2*R*)-2,4,33-trimethyl-29,29-dioxo-19,23,28-trioxa-29λ<sup>6</sup>-thia-1,14,15,16-tetraazahexacyclo[22.5.3.1<sup>3,7</sup>.1<sup>9,13</sup>.0<sup>12,16</sup>.0<sup>27,31</sup>]tetratriaconta-3(34),4,6,9(33),10,12,14,24,26,31-decaen-8-yl]acetate**

Using General Procedure 11 starting from ethyl 3-{1-[2-(3-bromopropoxy)ethyl]-4-methyl-1*H*-benzotriazol-5-yl}-3-{3-[(1*R*)-1-(6-hydroxy-2,2-dioxo-2*H*-1,2λ<sup>6</sup>,3-benzoxathiazin-3(4*H*)-

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yl)ethyl]-4-methylphenyl} propanoate (1 eq.) as a reactant, the title compound (white solid, 83% yield) was obtained.

<sup>1</sup>H-NMR (400 MHz, DMSO-d<sub>6</sub>) δ ppm: 1.00 (td, J=7.09, 5.50 Hz, 5 H) 1.24 (d, J=6.85 Hz, 2 H) 1.52 (d, J=6.85 Hz, 3 H) 1.77 - 1.86 (m, 1 H) 1.92 (dt, J=12.90, 6.39 Hz, 2 H) 2.30 (d, J=1.59 Hz, 5 H) 2.79 (s, 2 H) 2.85 (s, 3 H) 2.92 - 3.27 (m, 4 H) 3.44 - 3.66 (m, 5 H) 3.81 - 3.88 (m, 3 H) 3.92 - 4.01 (m, 3 H) 4.01 - 4.16 (m, 2 H) 4.34 (d, J=17.85 Hz, 1 H) 4.70 - 4.82 (m, 2 H) 4.82 - 4.96 (m, 3 H) 5.28 (d, J=7.09 Hz, 1 H) 5.35 (q, J=6.64 Hz, 1 H) 6.00 (d, J=2.81 Hz, 1 H) 6.44 (d, J=2.81 Hz, 1 H) 6.71 - 6.85 (m, 2 H) 6.91 - 7.02 (m, 2 H) 7.11 (d, J=7.82 Hz, 1 H) 7.19 - 7.31 (m, 2 H) 7.48 (d, J=6.85 Hz, 1 H) 7.57 (s, 1 H) 7.58 - 7.69 (m, 3 H)

10

#### STEP 5 : Preparation of EXAMPLE 27

Using General Procedure 12 starting from ethyl [(2*R*)-2,4,33-trimethyl-29,29-dioxo-19,23,28-trioxa-29λ<sup>6</sup>-thia-1,14,15,16-tetraazahexacyclo[22.5.3.1<sup>3,7</sup>.1<sup>9,13</sup>.0<sup>12,16</sup>.0<sup>27,31</sup>]tetratriaconta-3(34),4,6,9(33),10,12,14,24,26,31-decaen-8-yl]acetate (1 eq.) as a reactant, the title compound (white solid, 97% yield) was obtained.

15

The diastereo-pure products were obtained by chromatographic separation on chiral column.

#### Example 27a (2*R*,8*R*)

20 **HRMS** calculated for C<sub>31</sub>H<sub>34</sub>N<sub>4</sub>O<sub>7</sub>S: 606.2148; [M+H]<sup>+</sup> found: 607.2224 (δ=0.5 ppm)

<sup>1</sup>H-NMR (400 MHz, DMSO-d<sub>6</sub>) δ ppm: 12.2 (sl, 1 H), 7.6 (d, 1 H), 7.49 (dd, 1 H), 7.26 (d, 1 H), 7.19 (d, 1 H), 7 (d, 1 H), 6.95 (d, 1 H), 6.76 (dd, 1 H), 6.01 (d, 1 H), 5.28 (q, 1 H), 4.9 (t, 1 H), 4.78 (m, 2 H), 4.11/3.9 (d, 2 H), 4 (m, 2 H), 3.6 (m, 2 H), 3.55 (m, 2 H), 3.08/2.85 (dd, 2 H), 2.79 (s, 3 H), 2.3 (s, 3 H), 1.83 (m, 2 H), 1.23 (d, 3 H)

25

#### Example 27b (2*R*,8*S*)

**HRMS** calculated for C<sub>31</sub>H<sub>34</sub>N<sub>4</sub>O<sub>7</sub>S: 606.2148; [M+H]<sup>+</sup> found: 607.2222 (δ=0.2 ppm)

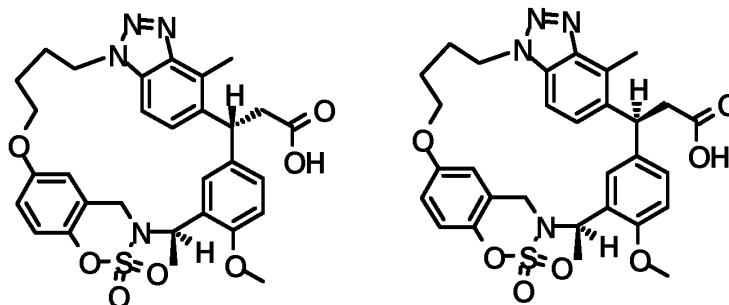
<sup>1</sup>H-NMR (400 MHz, DMSO-d<sub>6</sub>) δ ppm: 12.1 (sl, 1 H), 7.64 (d, 1 H), 7.59 (d, 1 H), 7.55 (d, 1 H), 7.23 (dd, 1 H), 7.11 (d, 1 H), 6.99 (d, 1 H), 6.81 (dd, 1 H), 6.43 (d, 1 H), 5.33 (q, 1 H),

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4.85/4.76 (m, 2 H), 4.85 (t, 1 H), 4.32/4.01 (d, 2 H), 4-3.97 (m, 2 H), 3.86 (m, 2 H), 3.61/3.52 (m, 2 H), 3.07 (m, 2 H), 2.83 (s, 3 H), 2.3 (s, 3 H), 1.91 (m, 2 H), 1.5 (d, 3 H)

**EXAMPLES 28a and 28b : [(2*R*,8*R*)-4-Methoxy-2,31-dimethyl-27,27-dioxo-21,26-dioxa-**

5 **27λ<sup>6</sup>-thia-1,14,15,16-tetraazahexacyclo**  
**[20.5.3.1<sup>3,7</sup>.1<sup>9,13</sup>.0<sup>12,16</sup>.0<sup>25,29</sup>]dotriaconta-**  
**3(32),4,6,9(31),10,12,14,22,24,29-decaen-8-yl]acetic acid and**  
**[(2*R*,8*S*)-4-methoxy-2,31-dimethyl-27,27-dioxo-21,26-dioxa-**  
**27λ<sup>6</sup>-thia-1,14,15,16-tetraazahexacyclo**  
10 **[20.5.3.1<sup>3,7</sup>.1<sup>9,13</sup>.0<sup>12,16</sup>.0<sup>25,29</sup>]dotriaconta-**  
**3(32),4,6,9(31),10,12,14,22,24,29-decaen-8-yl]acetic acid**



15 **STEP 1 : Preparation of ethyl 3-{3-[(1*S*)-1-hydroxyethyl]-4-methoxyphenyl}-3-(1-{4-[(4-methoxyphenyl)methoxy]butyl}-4-methyl-1*H*-benzotriazol-5-yl)propanoate**

Using General Procedure 6 starting from ethyl (2*E*)-3-(1-{4-[(4-methoxyphenyl)methoxy]butyl}-4-methyl-1*H*-benzotriazol-5-yl)prop-2-enoate (1 eq.) and  
20 (1*S*)-1-[2-methoxy-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]ethan-1-ol (1.5 eq.) as reactants, the title compound (65% yield) was obtained.

**<sup>1</sup>H-NMR** (400 MHz, DMSO-*d*<sub>6</sub>) δ ppm: 7.58 (2d, 1 H), 7.45 (2d, 1 H), 7.37 (d, 1 H), 7.2 (d, 2 H), 7.13 (2dd, 1 H), 6.87 (d, 2 H), 6.82 (d, 1 H), 4.91 (m, 1 H), 4.89 (d, 1 H), 4.82 (m, 1 H), 4.64

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(m, 2 H), 4.32 (s, 2 H), 3.92 (q, 2 H), 3.73/3.72 (2s, 6 H), 3.38 (t, 2 H), 3.11 (m, 2 H), 2.76/2.75 (2s, 3 H), 1.92 (m, 2 H), 1.48 (m, 2 H), 1.22-1.15 (2d, 3 H), 0.99 (t, 3 H)

**STEP 2 : Preparation of ethyl 3-(3-((1*R*)-1-[6-(benzyloxy)-2,2-dioxo-2*H*-1,2λ<sup>6</sup>,3-benzoxathiazin-3(4*H*)-yl]ethyl)-4-methoxyphenyl)-3-(1-{4-[(4-methoxyphenyl)methoxy]butyl}-4-methyl-1*H*-benzotriazol-5-yl)propanoate**

Using General Procedure 7 starting from ethyl 3-{3-[(1*S*)-1-hydroxyethyl]-4-methoxyphenyl}-3-(1-{4-[(4-methoxyphenyl)methoxy]butyl}-4-methyl-1*H*-benzotriazol-5-yl)propanoate (1 eq.) and 6-(benzyloxy)-3,4-dihydro-2*H*-1,2λ<sup>6</sup>,3-benzoxathiazine-2,2-dione (1.1 eq.) as reactants, the title compound (66% yield) was obtained.

**<sup>1</sup>H-NMR** (400 MHz, DMSO-d<sub>6</sub>) δ ppm: 7.6 (d, 1 H), 7.5 (2d, 1 H), 7.45-7.3 (m, 6 H), 7.2 (d, 2 H), 7.1 (dd, 1 H), 6.9 (m, 4 H), 6.75 (m, 2 H), 5.39 (m, 1 H), 5 (m, 2 H), 4.8 (m, 1 H), 4.6 (2t, 2 H), 4.55 (m, 2 H), 4.3 (s, 2 H), 3.91 (q, 2 H), 3.71/3.65 (2s, 6 H), 3.48 (m, 2 H), 3.18 (d, 2 H), 2.79 (s, 3 H), 1.91 (m, 2 H), 1.5 (m, 2 H), 1.45 (2d, 3 H), 1 (t, 3 H)

**STEP 3 : Preparation of ethyl 3-[1-(4-hydroxybutyl)-4-methyl-1*H*-benzotriazol-5-yl]-3-{3-[(1*R*)-1-(6-hydroxy-2,2-dioxo-2*H*-1,2λ<sup>6</sup>,3-benzoxathiazin-3(4*H*)-yl)ethyl]-4-methoxyphenyl}propanoate**

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Using General Procedure 8 starting from ethyl 3-(3-((1*R*)-1-[6-(benzyloxy)-2,2-dioxo-2*H*-1,2λ<sup>6</sup>,3-benzoxathiazin-3(4*H*)-yl]ethyl)-4-methoxyphenyl)-3-(1-{4-[(4-methoxyphenyl)methoxy]butyl}-4-methyl-1*H*-benzotriazol-5-yl)propanoate (1 eq.) as a reactant, the title compound (off-white solid, 83% yield) was obtained.

**<sup>1</sup>H-NMR** (400 MHz, DMSO-d<sub>6</sub>) δ ppm: 1.01 (td, J=7.09, 3.79 Hz, 3 H) 1.21 (dd, J=13.69, 5.99 Hz, 1 H) 1.31 - 1.39 (m, 2 H) 1.42 (t, J=6.42 Hz, 3 H) 1.91 (quint, J=7.31 Hz, 2 H) 2.76 (d, J=3.67 Hz, 3 H) 3.09 - 3.21 (m, 2 H) 3.38 (t, J=5.93 Hz, 2 H) 3.67 (s, 3 H) 3.70 (s, 1 H) 3.94 (q, J=7.09 Hz, 2 H) 4.34 - 4.57 (m, 3 H) 4.65 (t, J=6.97 Hz, 2 H) 4.83 (q, J=7.62 Hz, 1 H) 5.37 (quint, J=6.79 Hz, 1 H) 6.51 (dd, J=13.14, 2.75 Hz, 1 H) 6.64 (dd, J=8.99, 2.75 Hz, 1 H)

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6.73 - 6.85 (m, 3 H) 7.08 (d, J=8.19 Hz, 1 H) 7.13 (dd, J=8.56, 2.08 Hz, 1 H) 7.42 (dd, J=9.35, 2.02 Hz, 1 H) 7.53 (t, J=9.11 Hz, 1 H) 7.59 - 7.67 (m, 1 H) 9.54 (br. s., 1 H)

**STEP 4: Preparation of ethyl 3-[1-(4-bromobutyl)-4-methyl-1*H*-benzotriazol-5-yl]-3-{3-[(1*R*)-1-(6-hydroxy-2,2-dioxo-2*H*-1,2λ<sup>6</sup>,3-benzoxathiazin-3(4*H*)-yl)ethyl]-4-methoxyphenyl}propanoate**

Using General Procedure 9 starting from ethyl 3-[1-(4-hydroxybutyl)-4-methyl-1*H*-benzotriazol-5-yl]-3-{3-[(1*R*)-1-(6-hydroxy-2,2-dioxo-2*H*-1,2λ<sup>6</sup>,3-benzoxathiazin-3(4*H*)-yl)ethyl]-4-methoxyphenyl}propanoate (1 eq.) as a reactant, the title compound (73% yield) was obtained.

**<sup>1</sup>H-NMR** (400 MHz, DMSO-d<sub>6</sub>) δ ppm: 1.00 (td, J=7.09, 3.79 Hz, 3 H) 1.42 (t, J=6.66 Hz, 3 H) 1.71 - 1.83 (m, 2 H) 1.94 - 2.05 (m, 2 H) 2.70 - 2.79 (m, 3 H) 3.08 - 3.25 (m, 2 H) 3.53 (t, J=6.66 Hz, 2 H) 3.62 - 3.70 (m, 3 H) 3.94 (q, J=7.13 Hz, 2 H) 4.34 - 4.57 (m, 2 H) 4.69 (t, J=6.85 Hz, 2 H) 4.83 (q, J=7.83 Hz, 1 H) 5.31 - 5.42 (m, 1 H) 6.51 (dd, J=11.37, 2.81 Hz, 1 H) 6.64 (dd, J=8.93, 2.81 Hz, 1 H) 6.62 - 6.68 (m, 1 H) 6.74 - 6.84 (m, 2 H) 7.13 (dd, J=8.50, 2.02 Hz, 1 H) 7.42 (dd, J=10.03, 2.08 Hz, 1 H) 7.55 (t, J=8.74 Hz, 1 H) 7.61 - 7.68 (m, 1 H) 9.52 (d, J=5.01 Hz, 1 H)

**STEP 5 : Preparation of ethyl [(2*R*)-4-methoxy-2,31-dimethyl-27,27-dioxo-21,26-dioxo-27λ<sup>6</sup>-thia-1,14,15,16-tetraazahexacyclo[20.5.3.1<sup>3,7</sup>.1<sup>9,13</sup>.0<sup>12,16</sup>.0<sup>25,29</sup>]dotriacont-3(32),4,6,9(31),10,12,14,22,24,29-decaen-8-yl]acetate**

Using General Procedure 11 starting from ethyl 3-[1-(4-bromobutyl)-4-methyl-1*H*-benzotriazol-5-yl]-3-{3-[(1*R*)-1-(6-hydroxy-2,2-dioxo-2*H*-1,2λ<sup>6</sup>,3-benzoxathiazin-3(4*H*)-yl)ethyl]-4-methoxyphenyl}propanoate (1 eq.) as a reactant, the title compound (white solid, 73% yield) was obtained.

**<sup>1</sup>H-NMR** (400 MHz, DMSO-d<sub>6</sub>) δ ppm: 1.02 (td, J=7.09, 2.81 Hz, 6 H) 1.12 - 1.22 (m, 5 H) 1.22 - 1.29 (m, 4 H) 1.31 (d, J=7.21 Hz, 3 H) 1.40 (d, J=7.46 Hz, 1 H) 1.48 - 1.61 (m, 1 H) 1.62 - 1.88 (m, 2 H) 2.00 - 2.28 (m, 4 H) 2.63 - 2.90 (m, 6 H) 3.09 (td, J=15.62, 7.89 Hz, 2 H) 3.24 -



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3.37 (m, 10 H) 3.46 (td, J=9.54, 6.11 Hz, 1 H) 3.53 - 3.69 (m, 3 H) 3.70 - 3.80 (m, 7 H) 3.88 - 3.98 (m, 5 H) 4.05 - 4.15 (m, 1 H) 4.68 - 4.97 (m, 6 H) 5.43 (dq, J=17.93, 7.19 Hz, 2 H) 5.62 (d, J=2.57 Hz, 1 H) 5.75 (d, J=2.81 Hz, 1 H) 6.62 - 6.72 (m, 2 H) 6.80 - 6.94 (m, 4 H) 6.99 (d, J=8.56 Hz, 1 H) 7.20 - 7.29 (m, 2 H) 7.42 (dd, J=8.44, 1.96 Hz, 1 H) 7.50 (dd, J=8.56, 1.83 Hz, 1 H) 7.67 (d, J=8.68 Hz, 1 H) 7.74 - 7.81 (m, 1 H) 7.83 - 7.89 (m, 1 H)

#### STEP 6 : Preparation of EXAMPLES 28a and 28b

Using General Procedure 12 starting from ethyl [(2*R*)-4-methoxy-2,31-dimethyl-27,27-dioxo-21,26-dioxa-27 $\lambda^6$ -thia-1,14,15,16-tetraazahexacyclo[20.5.3.1<sup>3,7</sup>.1<sup>9,13</sup>.0<sup>12,16</sup>.0<sup>25,29</sup>]dotriaconta-3(32),4,6,9(31),10,12,14,22,24,29-decaen-8-yl]acetate (1 eq.) as a reactant, the title compound (white solid, 77% yield) was obtained.

The diastereo-pure products were obtained by chromatographic separation on chiral column.

#### 15 Example 28a (2*R*,8*R*)

HRMS calculated for C<sub>30</sub>H<sub>32</sub>N<sub>4</sub>O<sub>7</sub>S: 592.1992; [M+H]<sup>+</sup> found: 593.2067 ( $\delta$ =0.4 ppm)

<sup>1</sup>H-NMR (400 MHz, DMSO-d<sub>6</sub>)  $\delta$  ppm: 12.5-11.8 (m, 1 H), 7.67 (d, 1 H), 7.5 (dd, 1 H), 7.19 (d, 1 H), 7 (d, 1 H), 6.83 (d, 1 H), 6.8 (d, 1 H), 6.65 (dd, 1 H), 5.63 (d, 1 H), 5.4 (q, 1 H), 4.87 (dd, 1 H), 4.72 (m, 2 H), 4/3.71 (AM, 2 H), 3.76 (s, 3 H), 3.6/3.32 (2m, 2 H), 3.2/2.9 (2dd, 2 H), 2.81 (s, 3 H), 2.2/2.01 (2m, 2 H), 1.7/1.4 (2m, 2 H), 1.17 (d, 3 H)

#### Example 28b (2*R*,8*S*)

HRMS calculated for C<sub>30</sub>H<sub>32</sub>N<sub>4</sub>O<sub>7</sub>S: 592.1992; [M+H]<sup>+</sup> found: 593.2066 ( $\delta$ =0.3 ppm)

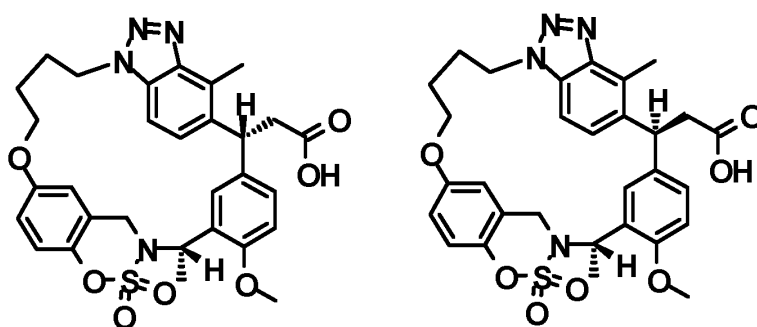
<sup>1</sup>H-NMR (400 MHz, DMSO-d<sub>6</sub>)  $\delta$  ppm: 12.3-11.6 (m, 1 H), 7.92 (dd, 1 H), 7.82 (d, 1 H), 7.77 (d, 1 H), 7.18 (d, 1 H), 6.9 (d, 1 H), 6.88 (d, 1 H), 6.69 (dd, 1 H), 5.7 (d, 1 H), 5.42 (q, 1 H), 4.75 (m, 3 H), 4.08/3.69 (AM, 2 H), 3.72 (s, 3 H), 3.62/3.45 (2m, 2 H), 3.2/2.99 (2dd, 2 H), 2.68 (s, 3 H), 2.2/2.1 (2m, 2 H), 1.8/1.59 (2m, 2 H), 1.29 (d, 3 H)

#### EXAMPLES 28c and 28d : [(2*S*,8*R*)-4-Methoxy-2,31-dimethyl-27,27-dioxo-21,26-dioxa-27 $\lambda^6$ -thia-1,14,15,16-

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tetraazahexacyclo[20.5.3.1<sup>3,7</sup>.1<sup>9,13</sup>.0<sup>12,16</sup>.0<sup>25,29</sup>]dotriaconta-3(32),4,6,9(31),10,12,14,22,24,29-decaen-8-yl]acetic acid and [(2*S*,8*S*)-4-methoxy-2,31-dimethyl-27,27-dioxo-21,26-dioxo-27λ<sup>6</sup>-thia-1,14,15,16-

5 tetraazahexacyclo[20.5.3.1<sup>3,7</sup>.1<sup>9,13</sup>.0<sup>12,16</sup>.0<sup>25,29</sup>]dotriaconta-3(32),4,6,9(31),10,12,14,22,24,29-decaen-8-yl]acetic acid



10 **STEP 1 : Preparation of ethyl 3-{3-[(1*R*)-1-hydroxyethyl]-4-methoxyphenyl}-3-(1-{4-[(4-methoxyphenyl)methoxy]butyl}-4-methyl-1*H*-benzotriazol-5-yl)propanoate**

Using General Procedure 6 starting from ethyl (2*E*)-3-(1-{4-[(4-methoxyphenyl)methoxy]butyl}-4-methyl-1*H*-benzotriazol-5-yl)prop-2-enoate (1 eq.) and  
 15 (1*R*)-1-[2-methoxy-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]ethan-1-ol (1.1 eq.) as reactants, the title compound (81% yield) was obtained.

<sup>1</sup>H-NMR (400 MHz, DMSO-d<sub>6</sub>) δ ppm: 7.6 (2d, 1 H), 7.45 (2d, 1 H), 7.35 (d, 1 H), 7.2 (d, 2 H), 7.12 (dd, 1 H), 6.88 (d, 2 H), 6.81 (d, 1 H), 4.9 (d, 1 H), 4.9 (m, 1 H), 4.8 (m, 1 H), 4.65 (t, 2 H), 4.32 (s, 2 H), 3.91 (q, 2 H), 3.71 (2s, 6 H), 3.4 (t, 2 H), 3.1 (2d, 2 H), 2.79 (2s, 3 H), 1.92  
 20 (m, 2 H), 1.48 (m, 2 H), 1.2 (2d, 3 H), 1 (t, 3 H)

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**STEP 2 : Preparation of ethyl 3-(3-((1*S*)-1-[6-(benzyloxy)-2,2-dioxo-2*H*-1,2λ<sup>6</sup>,3-benzoxathiazin-3(4*H*)-yl]ethyl)-4-methoxyphenyl)-3-(1-{4-[(4-methoxyphenyl)methoxy]butyl}-4-methyl-1*H*-benzotriazol-5-yl)propanoate**

5 Using General Procedure 7 starting from ethyl 3-{3-[(1*R*)-1-hydroxyethyl]-4-methoxyphenyl}-3-(1-{4-[(4-methoxyphenyl)methoxy]butyl}-4-methyl-1*H*-benzotriazol-5-yl)propanoate (1 eq.) and 6-benzyloxy-3,4-dihydro-1,2λ<sup>6</sup>,3-benzoxathiazine 2,2-dioxide (1.1eq.) as reactants, the title compound (60% yield) was obtained.

<sup>1</sup>H-NMR (400 MHz, DMSO-d<sub>6</sub>) δ ppm: 7.6 (d, 1 H), 7.5 (2d, 1 H), 7.45-7.3 (m, 6 H), 7.2 (d, 10 2 H), 7.11 (dd, 1 H), 6.9 (m, 2 H), 6.88 (d, 2 H), 6.78 (m, 2 H), 5.39 (m, 1 H), 5.05 (m, 2 H), 4.81 (m, 1 H), 4.65-4.5 (m, 2 H), 4.61 (2t, 2 H), 4.3 (s, 2 H), 3.92 (q, 2 H), 3.71/3.65 (2s, 6 H), 3.38 (m, 2 H), 3.15 (m, 2 H), 2.78 (s, 3 H), 1.9 (m, 2 H), 1.48 (m+d, 5 H), 0.99 (t, 3 H)

**STEP 3 : Preparation of ethyl 3-[1-(4-hydroxybutyl)-4-methyl-1*H*-benzotriazol-5-yl]-3-{3-[(1*S*)-1-(6-hydroxy-2,2-dioxo-2*H*-1,2λ<sup>6</sup>,3-benzoxathiazin-3(4*H*)-yl)ethyl]-4-methoxyphenyl}propanoate**

Using General Procedure 8 starting from ethyl 3-(3-((1*S*)-1-[6-(benzyloxy)-2,2-dioxo-2*H*-1,2λ<sup>6</sup>,3-benzoxathiazin-3(4*H*)-yl]ethyl)-4-methoxyphenyl)-3-(1-{4-[(4-methoxyphenyl)methoxy]butyl}-4-methyl-1*H*-benzotriazol-5-yl)propanoate (1 eq.) as a 20 reactant, the title compound (70% yield) was obtained.

<sup>1</sup>H-NMR (400 MHz, DMSO-d<sub>6</sub>) δ ppm: 0.95 - 1.03 (m, 3 H) 1.30 - 1.47 (m, 5 H) 1.85 - 1.97 (m, 2 H) 2.76 (d, J=3.55 Hz, 3 H) 3.18 (d, J=8.19 Hz, 2 H) 3.34 - 3.42 (m, 2 H) 3.67 (s, 3 H) 3.94 (q, J=7.13 Hz, 2 H) 4.33 (t, J=5.07 Hz, 1 H) 4.37 - 4.58 (m, 3 H) 4.65 (t, J=6.97 Hz, 2 H) 25 4.83 (q, J=7.87 Hz, 1 H) 5.32 - 5.42 (m, 1 H) 6.51 (dd, J=13.20, 2.81 Hz, 1 H) 6.64 (dd, J=8.86, 2.75 Hz, 1 H) 6.76 (d, J=1.59 Hz, 1 H) 6.79 - 6.84 (m, 2 H) 7.08 (d, J=8.31 Hz, 1 H) 7.13 (dd, J=8.56, 2.08 Hz, 1 H) 7.42 (dd, J=9.05, 1.96 Hz, 1 H) 7.53 (t, J=9.17 Hz, 1 H) 7.60 - 7.65 (m, 1 H) 9.51 (s, 1 H) 9.52 (s, 1 H)

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**STEP 4 : Preparation of ethyl 3-[1-(4-bromobutyl)-4-methyl-1*H*-benzotriazol-5-yl]-3-{3-[(1*S*)-1-(6-hydroxy-2,2-dioxo-2*H*-1,2λ<sup>6</sup>,3-benzoxathiazin-3(4*H*)-yl)ethyl]-4-methoxyphenyl}propanoate**

5 Using General Procedure 9 starting from ethyl 3-[1-(4-hydroxybutyl)-4-methyl-1*H*-benzotriazol-5-yl]-3-{3-[(1*S*)-1-(6-hydroxy-2,2-dioxo-2*H*-1,2λ<sup>6</sup>,3-benzoxathiazin-3(4*H*)-yl)ethyl]-4-methoxyphenyl}propanoate (1 eq.) as a reactant, the title compound (white solid, quant.) was obtained.

<sup>1</sup>**H-NMR** (400 MHz, DMSO-d<sub>6</sub>) δ ppm: 1.00 (td, J=7.09, 3.79 Hz, 3 H) 1.42 (t, J=6.66 Hz, 3 H) 1.71 - 1.82 (m, 2 H) 1.92 - 2.06 (m, 2 H) 2.76 (d, J=3.91 Hz, 3 H) 3.10 - 3.25 (m, 2 H) 3.53 (t, J=6.66 Hz, 2 H) 3.67 (d, J=1.10 Hz, 3 H) 3.94 (q, J=7.13 Hz, 2 H) 4.35 - 4.60 (m, 2 H) 4.69 (t, J=6.85 Hz, 2 H) 4.83 (q, J=7.83 Hz, 1 H) 5.36 (quin, J=6.94 Hz, 1 H) 6.51 (dd, J=11.37, 2.81 Hz, 1 H) 6.64 (dd, J=8.93, 2.81 Hz, 1 H) 6.76 (s, 1 H) 6.78 (s, 1 H) 6.81 (dd, J=8.68, 2.93 Hz, 1 H) 7.13 (dd, J=8.50, 2.02 Hz, 1 H) 7.42 (dd, J=10.03, 2.08 Hz, 1 H) 7.55 (t, J=8.74 Hz, 1 H) 7.61 - 7.69 (m, 1 H) 9.52 (d, J=5.01 Hz, 1 H)

**STEP 5 : Preparation of ethyl [(2*S*)-4-methoxy-2,31-dimethyl-27,27-dioxo-21,26-dioxo-27λ<sup>6</sup>-thia-1,14,15,16-tetraazahexacyclo[20.5.3.1<sup>3,7</sup>.1<sup>9,13</sup>.0<sup>12,16</sup>.0<sup>25,29</sup>]dotriacont-3(32),4,6,9(31),10,12,14,22,24,29-decaen-8-yl]acetate**

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Using General Procedure 11 starting from ethyl 3-[1-(4-bromobutyl)-4-methyl-1*H*-benzotriazol-5-yl]-3-{3-[(1*S*)-1-(6-hydroxy-2,2-dioxo-2*H*-1,2λ<sup>6</sup>,3-benzoxathiazin-3(4*H*)-yl)ethyl]-4-methoxyphenyl}propanoate (1 eq.) as a reactant, the title compound (white solid, 60% yield) was obtained.

<sup>1</sup>**H-NMR** (400 MHz, DMSO-d<sub>6</sub>) δ ppm: 0.98 - 1.07 (m, 6 H) 1.15 - 1.20 (m, 4 H) 1.31 (d, J=7.21 Hz, 3 H) 1.40 (d, J=7.46 Hz, 1 H) 1.48 - 1.61 (m, 1 H) 1.62 - 1.75 (m, 1 H) 1.75 - 1.87 (m, 1 H) 2.00 - 2.14 (m, 2 H) 2.14 - 2.28 (m, 2 H) 2.70 (s, 3 H) 2.84 (s, 2 H) 3.09 (td, J=15.62, 7.89 Hz, 2 H) 3.32 - 3.38 (m, 1 H) 3.46 (td, J=9.54, 6.11 Hz, 1 H) 3.54 - 3.77 (m, 9 H) 3.87 - 3.98 (m, 5 H) 3.98 - 4.02 (m, 1 H) 4.05 - 4.14 (m, 1 H) 4.66 - 4.83 (m, 5 H) 4.89 (t, J=7.89 Hz, 1 H) 5.43 (dq, J=17.93, 7.19 Hz, 2 H) 5.62 (d, J=2.57 Hz, 1 H) 5.75 (d, J=2.81 Hz, 1 H) 6.62 -

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6.72 (m, 2 H) 6.81 - 6.93 (m, 4 H) 6.99 (d, J=8.56 Hz, 1 H) 7.19 - 7.26 (m, 2 H) 7.42 (dd, J=8.44, 1.96 Hz, 1 H) 7.50 (dd, J=8.56, 1.83 Hz, 1 H) 7.67 (d, J=8.68 Hz, 1 H) 7.74 - 7.80 (m, 1 H) 7.83 - 7.89 (m, 1 H)

## 5 STEP 6 : Preparation of EXAMPLES 28c and 28d

Using General Procedure 12 starting from ethyl [(2*S*)-4-methoxy-2,31-dimethyl-27,27-dioxo-21,26-dioxa-27 $\lambda^6$ -thia-1,14,15,16-tetraazahexacyclo[20.5.3.1<sup>3,7</sup>.1<sup>9,13</sup>.0<sup>12,16</sup>.0<sup>25,29</sup>]dotriaconta-3(32),4,6,9(31),10,12,14,22,24,29-decaen-8-yl]acetate (1 eq.) as a reactant, the title compound  
10 (white solid, 89% yield) was obtained.

The diastereo-pure products were obtained by chromatographic separation on chiral column.

### Example 28c (2*S*,8*R*)

HRMS calculated for C<sub>30</sub>H<sub>32</sub>N<sub>4</sub>O<sub>7</sub>S: 592.1992; [M+H]<sup>+</sup> found: 593.2065 ( $\delta$ =0.1 ppm)

15

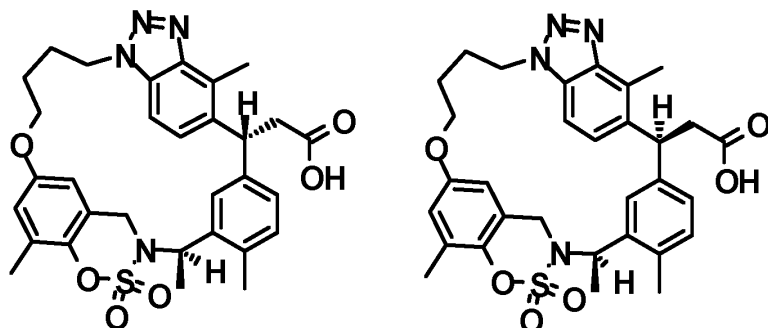
### Example 28d (2*S*,8*S*)

HRMS calculated for C<sub>30</sub>H<sub>32</sub>N<sub>4</sub>O<sub>7</sub>S: 592.1992; [M+H]<sup>+</sup> found: 593.2070 ( $\delta$ =0.9 ppm)

<sup>1</sup>H-NMR (400 MHz, DMSO-d<sub>6</sub>)  $\delta$  ppm: 12.3-11.6 (m, 1 H), 7.92 (dd, 1 H), 7.82 (d, 1 H), 7.77 (d, 1 H), 7.18 (d, 1 H), 6.9 (d, 1 H), 6.88 (d, 1 H), 6.69 (dd, 1 H), 5.7 (d, 1 H), 5.42 (q, 1 H),  
20 4.75 (m, 3 H), 4.08/3.69 (AM, 2 H), 3.72 (s, 3 H), 3.62/3.45 (m, 2 H), 3.2/2.99 (dd, 2 H), 2.68 (s, 3 H), 2.2/2.1 (m, 2 H), 1.8/1.59 (m, 2 H), 1.29 (d, 3 H)

**EXAMPLE 29 : [(2*R*,8*R*)-2,4,24,31-Tetramethyl-27,27-dioxo-21,26-dioxa-27 $\lambda^6$ -thia-1,14,15,16-tetraazahexacyclo[20.5.3.1<sup>3,7</sup>.1<sup>9,13</sup>.0<sup>12,16</sup>.0<sup>25,29</sup>]dotriaconta-3(32),4,6,9(31),10,12,14,22,24,29-decaen-8-yl]acetic acid and [(2*R*,8*S*)-2,4,24,31-tetramethyl-27,27-dioxo-21,26-dioxa-27 $\lambda^6$ -thia-1,14,15,16-tetraazahexacyclo[20.5.3.1<sup>3,7</sup>.1<sup>9,13</sup>.0<sup>12,16</sup>.0<sup>25,29</sup>]dotriaconta-3(32),4,6,9(31),10,12,14,22,24,29-decaen-8-yl]acetic acid**  
25

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**STEP 1: Preparation of ethyl 3-{1-[4-(benzyloxy)butyl]-4-methyl-1*H*-benzotriazol-5-yl}-3-[3-[(1*S*)-1-hydroxyethyl]-4-methylphenyl]propanoate**

5

Using General Procedure 6 starting from ethyl (E)-3-[1-(4-benzyloxybutyl)-4-methylbenzotriazol-5-yl]prop-2-enoate (1 eq.) and (1S)-1-[2-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]ethanol (1.2 eq.) as reactants, the title compound (50% yield) was obtained.

<sup>1</sup>H-NMR (400 MHz, DMSO-d<sub>6</sub>) δ ppm: 7.58/7.46 (2dd, 1 H), 7.41 (d, 1 H), 7.35-7.22 (m, 5 H), 7.06 (dd, 1 H), 6.98 (d, 1 H), 4.97/4.96 (2d, 1 H), 4.83 (m, 1 H), 4.83 (m, 1 H), 4.65 (t, 2 H), 4.4 (s, 2 H), 3.92 (q, 2 H), 3.42 (t, 2 H), 3.12 (m, 2 H), 2.77/2.76 (2s, 3 H), 2.19 (s, 3 H), 1.94 (m, 2 H), 1.5 (m, 2 H), 1.23/1.21 (2d, 3 H), 1 (t, 3 H)

15     **STEP 2 : Preparation of ethyl 3-{1-[4-(benzyloxy)butyl]-4-methyl-1*H*-benzotriazol-5-yl}-3-(3-((1*R*)-1-[6-(benzyloxy)-8-methyl-2,2-dioxo-2*H*-1,2λ<sup>6</sup>,3-benzoxathiazin-3(4*H*)-yl]ethyl)-4-methylphenyl)propanoate**

Using General Procedure 7 starting from ethyl 3-{1-[4-(benzyloxy)butyl]-4-methyl-1*H*-  
20 benzotriazol-5-yl}-3-{3-[(1*S*)-1-hydroxyethyl]-4-methylphenyl} propanoate (1 eq.) and 6-  
(benzyloxy)-8-methyl-3,4-dihydro-2*H*-1,2λ<sup>6</sup>,3-benzoxathiazine-2,2-dione (1.1 eq.) as  
reactants, the title compound (68% yield) was obtained.

**<sup>1</sup>H-NMR** (400 MHz, DMSO-d<sub>6</sub>) δ ppm: 0.90 - 1.03 (m, 6 H) 1.41 (d, J=6.97 Hz, 5 H) 1.43 -

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1.53 (m, 4 H) 1.81 - 1.98 (m, 4 H) 2.13 - 2.20 (m, 6 H) 2.28 (s, 6 H) 2.73 - 2.80 (m, 6 H) 3.11 - 3.25 (m, 4 H) 3.34 - 3.44 (m, 4 H) 3.92 (q, J=7.05 Hz, 4 H) 4.25 - 4.37 (m, 2 H) 4.39 (d, J=3.67 Hz, 5 H) 4.55 - 4.66 (m, 4 H) 4.81 - 4.91 (m, 2 H) 4.99 - 5.11 (m, 4 H) 5.26 (q, J=6.93 Hz, 2 H) 6.63 (d, J=2.81 Hz, 1 H) 6.69 (d, J=2.81 Hz, 1 H) 6.89 - 6.97 (m, 2 H) 7.06 - 7.15 (m, 4 H) 7.20 - 7.37 (m, 12 H) 7.37 - 7.48 (m, 10 H) 7.51 - 7.56 (m, 2 H) 7.56 - 7.61 (m, 2 H)

**STEP 3 : Preparation of ethyl 3-[1-(4-hydroxybutyl)-4-methyl-1*H*-benzotriazol-5-yl]-3-{3-[(1*R*)-1-(6-hydroxy-8-methyl-2,2-dioxo-2*H*-1,2λ<sup>6</sup>,3-benzoxathiazin-3(4*H*)-yl)ethyl]-4-methylphenyl}propanoate**

10

Using General Procedure 8 starting from ethyl 3-{1-[4-(benzyloxy)butyl]-4-methyl-1*H*-benzotriazol-5-yl}-3-{3-[(1*R*)-1-[6-(benzyloxy)-8-methyl-2,2-dioxo-2*H*-1,2λ<sup>6</sup>,3-benzoxathiazin-3(4*H*)-yl]ethyl]-4-methylphenyl}propanoate (1 eq.) as a reactant, the title compound (63% yield) was obtained.

15

<sup>1</sup>H-NMR (400 MHz, DMSO-d<sub>6</sub>) δ ppm: 9.5/4.4 (s+t, 2 H), 7.61 (2d, 1 H), 7.58 (2d, 1 H), 7.45 (2d, 1 H), 7.11 (m, 2 H), 6.61 (2d, 1 H), 6.41/6.39 (2d, 1 H), 5.25 (m, 1 H), 4.9 (m, 1 H), 4.65 (t, 2 H), 4.35/4.29 (2m, 2 H), 3.95 (q, 2 H), 3.4 (q, 2 H), 3.21 (d, 2 H), 2.79 (s, 3 H), 2.3 (s, 3 H), 2.11 (2s, 3 H), 1.91 (m, 2 H), 1.45 (2d, 3 H), 1.38 (m, 2 H), 1.01 (2t, 3 H)

20

**STEP 4 : Preparation of ethyl 3-[1-(4-bromobutyl)-4-methyl-1*H*-benzotriazol-5-yl]-3-{3-[(1*R*)-1-(6-hydroxy-8-methyl-2,2-dioxo-2*H*-1,2λ<sup>6</sup>,3-benzoxathiazin-3(4*H*)-yl)ethyl]-4-methylphenyl}propanoate**

Using General Procedure 9 starting from ethyl 3-[1-(4-hydroxybutyl)-4-methyl-1*H*-benzotriazol-5-yl]-3-{3-[(1*R*)-1-(6-hydroxy-8-methyl-2,2-dioxo-2*H*-1,2λ<sup>6</sup>,3-benzoxathiazin-3(4*H*)-yl)ethyl]-4-methylphenyl}propanoate (1 eq.) as a reactant, the title compound (white solid, 77% yield) was obtained.

<sup>1</sup>H-NMR (400 MHz, DMSO-d<sub>6</sub>) δ ppm: 9.5 (s, 1 H), 7.62 (d, 1 H), 7.59 (d, 1 H), 7.48/7.41 (d, 1 H), 7.1 (m, 2 H), 6.61 (d, 1 H), 6.4/6.39 (d, 1 H), 5.24 (m, 1 H), 4.88 (m, 1 H), 4.69 (t, 2 H),

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4.31/4.28 (m, 2 H), 3.92 (q, 2 H), 3.52 (q, 2 H), 3.21 (d, 2 H), 2.79 (s, 3 H), 2.28 (s, 3 H), 2.1 (s, 2 H), 2 (m, 2 H), 1.78 (d, 3 H), 1.41 (m, 2 H), 1 (t, 3 H)

**STEP 5 : Preparation of ethyl [(2*R*)-2,4,24,31-tetramethyl-27,27-dioxo-21,26-dioxa-27 $\lambda^6$ -thia-1,14,15,16-tetraazahexacyclo[20.5.3.1<sup>3,7</sup>.1<sup>9,13</sup>.0<sup>12,16</sup>.0<sup>25,29</sup>]dotriaconta-3(32),4,6,9(31),10,12,14,22,24,29-decaen-8-yl]acetate**

Using General Procedure 11 starting from ethyl 3-[1-(4-bromobutyl)-4-methyl-1*H*-benzotriazol-5-yl]-3-{3-[(1*R*)-1-(6-hydroxy-8-methyl-2,2-dioxo-2*H*-1,2 $\lambda^6$ ,3-benzoxathiazin-3(4*H*)-yl)ethyl]-4-methylphenyl}propanoate (1 eq.) as a reactant, the title compound (white solid, 61% yield) was obtained.

**<sup>1</sup>H-NMR** (400 MHz, DMSO-*d*<sub>6</sub>)  $\delta$  ppm: 0.97 - 1.13 (m, 4 H) 1.21 - 1.32 (m, 2 H) 1.53 - 1.76 (m, 1 H) 1.77 - 1.89 (m, 1 H) 2.03 - 2.10 (m, 3 H) 2.12 - 2.25 (m, 1 H) 2.31 (d, *J*=11.86 Hz, 3 H) 2.66 (s, 2 H) 2.72 - 2.80 (m, 1 H) 2.81 (s, 1 H) 2.95 - 3.15 (m, 1 H) 3.34 - 3.51 (m, 2 H) 3.67 (td, *J*=9.75, 5.32 Hz, 1 H) 3.88 - 4.01 (m, 3 H) 4.62 - 4.85 (m, 3 H) 4.92 (t, *J*=7.76 Hz, 1 H) 5.24 (dq, *J*=13.89, 6.82 Hz, 1 H) 5.53 (d, *J*=2.93 Hz, 1 H) 5.69 (br. s., 1 H) 6.56 - 6.76 (m, 1 H) 7.08 - 7.24 (m, 2 H) 7.30 (d, *J*=7.95 Hz, 1 H) 7.44 (d, *J*=7.70 Hz, 1 H) 7.68 (d, *J*=8.80 Hz, 1 H) 7.74 (d, *J*=8.68 Hz, 1 H) 7.88 (d, *J*=8.68 Hz, 1 H)

**STEP 6 : Preparation of EXAMPLE 29**

Using General Procedure 12 starting from ethyl [(2*R*)-2,4,24,31-tetramethyl-27,27-dioxo-21,26-dioxa-27 $\lambda^6$ -thia-1,14,15,16-tetraazahexacyclo[20.5.3.1<sup>3,7</sup>.1<sup>9,13</sup>.0<sup>12,16</sup>.0<sup>25,29</sup>]dotriaconta-3(32),4,6,9(31),10,12,14,22,24,29-decaen-8-yl]acetate (1 eq.) as a reactant, the title compound (white solid, 73% yield) was obtained.

The diastereo-pure products were obtained by chromatographic separation on chiral column.

**Example 29a (2*R*,8*R*)**

**HRMS** calculated for C<sub>31</sub>H<sub>34</sub>N<sub>4</sub>O<sub>6</sub>S: 590.2199; [M+H]<sup>+</sup> found: 591.2273 ( $\delta$ =0.2 ppm)



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<sup>1</sup>H-NMR (400 MHz, DMSO-d<sub>6</sub>) δ ppm: 12.25 (m, 1 H), 7.7 (d, 1 H), 7.48 (dd, 1 H), 7.3 (d, 1 H), 7.1 (d, 1 H), 6.72 (d, 1 H), 6.61 (d, 1 H), 5.7 (sl, 1 H), 5.21 (q, 1 H), 4.9 (t, 1 H), 4.75 (m, 2 H), 4.02/3.48 (2d, 2 H), 3.75/3.7 (2m, 2 H), 3.28/2.9 (2dd, 2 H), 2.8 (s, 3 H), 2.31 (s, 3 H), 2.2/2.02 (2m, 2 H), 2.08 (s, 3 H), 1.61/1.28 (2m, 2 H), 1.11 (d, 3 H)

5

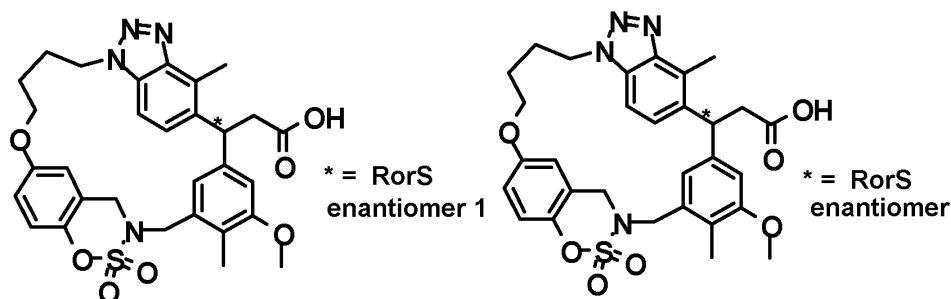
**Example 29b (2R,8S)**

HRMS calculated for C<sub>31</sub>H<sub>34</sub>N<sub>4</sub>O<sub>6</sub>S: 590.2199; [M+H]<sup>+</sup> found: 591.2273 (δ=0.2 ppm)

<sup>1</sup>H-NMR (400 MHz, DMSO-d<sub>6</sub>) δ ppm: 12.2 (m, 1 H), 7.89 (d, 1 H), 7.72 (d, 1 H), 7.48 (dd, 1 H), 7.2 (d, 1 H), 7.11 (d, 1 H), 6.69 (d, 1 H), 5.51 (d, 1 H), 5.28 (q, 1 H), 4.8-4.7 (2m, 2 H), 4.8 (t, 1 H), 4/3.4 (2d, 2 H), 3.65/3.47 (2m, 2 H), 3.2/2.99 (2dd, 2 H), 2.69 (s, 3 H), 2.3 (s, 3 H), 2.18/2.1 (2m, 2 H), 2.1 (s, 3 H), 1.82/1.71 (2m, 2 H), 1.11 (d, 3 H)

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**EXAMPLE 30 : [5-Methoxy-4,31-dimethyl-27,27-dioxo-21,26-dioxa-27λ<sup>6</sup>-thia-1,14,15,16-tetraazahexacyclo[20.5.3.1<sup>3,7</sup>.1<sup>9,13</sup>.0<sup>12,16</sup>.0<sup>25,29</sup>]dotriacont-3(32),4,6,9(31),10,12,14,22,24,29-decaen-8-yl]acetic acid**

**STEP B1 : Preparation of methyl 5-bromo-3-methoxy-2-methylbenzoate**

20

Methyl 5-bromo-3-hydroxy-2-methylbenzoate (1.0 eq., 26.0 g, 106.1 mmol) was dissolved in DMF (300 mL), then methyl iodide (4 eq., 26.5 mL, 60.2 g, 424.5 mmol) and Cs<sub>2</sub>CO<sub>3</sub> (4 eq., 137.9 g, 424.5 mmol) were added. The reaction mixture was stirred at RT for 12h. After the completion of the reaction the mixture was poured into ice water, extracted with EtOAc, after

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separation the organic phase was dried over MgSO<sub>4</sub> and concentrated under reduced pressure. The crude product was purified by normal phase silica gel chromatography using heptane-EtOAc eluent to give the title compound (light yellow solid, 19.1 g, 69% yield).

<sup>1</sup>H-NMR (400 MHz, DMSO-d<sub>6</sub>) δ ppm: 7.44 (s, 1 H), 7.34 (s, 1 H), 3.88 (s, 3 H), 3.83 (s, 3 H), 2.25 (s, 3 H)

#### STEP B2 : Preparation of (5-bromo-3-methoxy-2-methylphenyl)methanol

Methyl 5-bromo-3-methoxy-2-methylbenzoate (1 eq., 19.0 g, 73 mmol) was dissolved in THF (200 mL), the solution was cooled to 0 °C. Lithium tetrahydrido aluminate (1.2 eq., 44mL, 2M solution in THF) was added over 30 min. under N<sub>2</sub> atm. the mixture was allowed to warm to RT and stirred at RT for 2h. The reaction mixture was quenched with aq. sat. NH<sub>4</sub>Cl solution, extracted with EtOAc, the organic phase was separated, dried over MgSO<sub>4</sub>, concentrated under reduced pressure. The crude product was purified by normal phase silica gel chromatography using heptane-EtOAc eluent to give the title compound (yellow solid, 14.7 g, 87 % yield).

<sup>1</sup>H-NMR (400 MHz, DMSO-d<sub>6</sub>) δ ppm: 7.16 (s, 1 H), 7.03 (s, 1 H), 5.23 (t, 1 H), 4.46 (d, 2 H), 3.34 (s, 3 H), 2.00 (s, 3 H)

#### STEP B3 : Preparation of [3-methoxy-2-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]methanol

Using General Procedure 3 starting from (5-bromo-3-methoxy-2-methylphenyl)methanol (1 eq., 14.6 g., 63 mmol) as a reactant, gave the title compound (12.53 g, 71% yield).

<sup>1</sup>H-NMR (400 MHz, DMSO-d<sub>6</sub>) δ ppm: 7.37 (sl, 1 H), 7.06 (sl, 1 H), 5.04 (t, 1 H), 4.47 (d, 2 H), 3.79 (s, 3 H), 2.09 (s, 3 H), 1.29 (s, 12 H)

#### STEP 1 : Preparation of ethyl 3-{1-[4-(benzyloxy)butyl]-4-methyl-1H-benzotriazol-5-yl}-3-[3-(hydroxymethyl)-5-methoxy-4-methylphenyl]propanoate

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Using General Procedure 6 starting from ethyl (2*E*)-3-{1-[4-(benzyloxy)butyl]-4-methyl-1*H*-benzotriazol-5-yl}prop-2-enoate (1 eq.) and [3-methoxy-2-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]methanol (1.15 eq.) as reactants, the title compound (76% yield) was obtained.

- 5 <sup>1</sup>H-NMR (400 MHz, DMSO-d<sub>6</sub>) δ ppm: 7.59 (d, 1 H), 7.49 (d, 1 H), 7.35-7.2 (m, 5 H), 6.89 (d, 2 H), 4.95 (t, 1 H), 4.82 (t, 1 H), 4.67 (t, 2 H), 4.41 (s, 2 H), 4.4 (d, 2 H), 3.91 (q, 2 H), 3.75 (s, 3 H), 3.45 (t, 2 H), 3.15 (d, 2 H), 2.8 (s, 3 H), 2 (s, 3 H), 1.95 (m, 2 H), 1.5 (m, 2 H), 1 (t, 3 H)

10 **STEP 2: Preparation of ethyl 3-{1-[4-(benzyloxy)butyl]-4-methyl-1*H*-benzotriazol-5-yl}-3-(3-{[6-(benzyloxy)-2,2-dioxo-2*H*-1,2λ<sup>6</sup>,3-benzoxathiazin-3(4*H*)-yl]methyl}-5-methoxy-4-methylphenyl)propanoate**

Using General Procedure 7 starting from ethyl 3-{1-[4-(benzyloxy)butyl]-4-methyl-1*H*-benzotriazol-5-yl}-3-[3-(hydroxymethyl)-5-methoxy-4-methylphenyl]propanoate (1 eq.) and  
15 6-(benzyloxy)-3,4-dihydro-2*H*-1,2λ<sup>6</sup>,3-benzoxathiazine-2,2-dione (1.1 eq.) as reactants, the title compound (87% yield) was obtained.

- <sup>1</sup>H-NMR (400 MHz, DMSO-d<sub>6</sub>) δ ppm: 7.59 (d, 1 H), 7.54 (d, 1 H), 7.49-7.2 (m, 10 H), 7.11 (d, 1 H), 7.08 (dd, 1 H), 6.96 (d, 1 H), 6.9 (d, 1 H), 6.8 (d, 1 H), 5.1 (s, 2 H), 4.87 (t, 1 H), 4.61 (t, 2 H), 4.39 (s, 4 H), 4.19 (m, 2 H), 3.92 (q, 2 H), 3.74 (s, 3 H), 3.39 (t, 2 H), 3.19 (d, 2 H),  
20 2.79 (s, 3 H), 2.03 (s, 3 H), 1.9 (m, 2 H), 1.48 (m, 2 H), 0.99 (t, 3 H)

**STEP 3: Preparation of ethyl 3-[1-(4-hydroxybutyl)-4-methyl-1*H*-benzotriazol-5-yl]-3-{3-[(6-hydroxy-2,2-dioxo-2*H*-1,2λ<sup>6</sup>,3-benzoxathiazin-3(4*H*)-yl)methyl]-5-methoxy-4-methylphenyl}propanoate**

25

Using General Procedure 8 starting from ethyl 3-{1-[4-(benzyloxy)butyl]-4-methyl-1*H*-benzotriazol-5-yl}-3-(3-{[6-(benzyloxy)-2,2-dioxo-2*H*-1,2λ<sup>6</sup>,3-benzoxathiazin-3(4*H*)-yl]methyl}-5-methoxy-4-methylphenyl)propanoate (1 eq.) as a reactant, the title compound (95% yield) was obtained.

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<sup>1</sup>H-NMR (400 MHz, DMSO-d<sub>6</sub>) δ ppm: 9.7/4.85 (s+t, 2 H), 7.6 (d, 1 H), 7.52 (d, 1 H), 7 (d, 1 H), 6.95 (d, 1 H), 6.8 (m, 2 H), 6.59 (d, 1 H), 4.65 (t, 2 H), 4.41 (m, 1 H), 4.31 (s, 2 H), 4.18 (m, 2 H), 3.95 (q, 2 H), 3.78 (s, 3 H), 3.4 (t, 2 H), 3.2 (d, 2 H), 2.8 (s, 3 H), 2.05 (s, 3 H), 1.91 (m, 2 H), 1.38 (m, 2 H), 1 (t, 3 H)

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**STEP 4 : Preparation of ethyl 3-[1-(4-bromobutyl)-4-methyl-1H-benzotriazol-5-yl]-3-{3-[(6-hydroxy-2,2-dioxo-2H-1,2λ<sup>6</sup>,3-benzoxathiazin-3(4H)-yl)methyl]-5-methoxy-4-methylphenyl}propanoate**

10 Using General Procedure 9 starting from ethyl 3-[1-(4-hydroxybutyl)-4-methyl-1H-benzotriazol-5-yl]-3-{3-[(6-hydroxy-2,2-dioxo-2H-1,2λ<sup>6</sup>,3-benzoxathiazin-3(4H)-yl)methyl]-5-methoxy-4-methylphenyl}propanoate (1 eq.) as a reactant, the title compound (white solid, 86% yield) was obtained.

15 <sup>1</sup>H-NMR (400 MHz, DMSO-d<sub>6</sub>) δ ppm: 9.67 (s, 1 H), 7.63 (d, 1 H), 7.56 (d, 1 H), 6.98 (d, 1 H), 6.95 (d, 1 H), 6.78 (m, 2 H), 6.57 (d, 1 H), 4.84 (t, 1 H), 4.69 (t, 2 H), 4.33 (s, 2 H), 4.2/4.12 (2d, 2 H), 3.94 (q, 2 H), 3.75 (s, 3 H), 3.53 (t, 2 H), 3.19 (d, 2 H), 2.78 (s, 3 H), 2.05 (s, 3 H), 2 (quint, 2 H), 1.77 (quint, 2 H), 1 (t, 3 H)

20 **STEP 5 : Preparation of ethyl [5-methoxy-4,31-dimethyl-27,27-dioxo-21,26-dioxa-27λ<sup>6</sup>-thia-1,14,15,16-tetraazahexacyclo[20.5.3.1<sup>3,7</sup>.1<sup>9,13</sup>.0<sup>12,16</sup>.0<sup>25,29</sup>]dotriaconta-3(32),4,6,9(31),10,12,14,22,24,29-decaen-8-yl]acetate**

25 Using General Procedure 11 starting from ethyl 3-[1-(4-bromobutyl)-4-methyl-1H-benzotriazol-5-yl]-3-{3-[(6-hydroxy-2,2-dioxo-2H-1,2λ<sup>6</sup>,3-benzoxathiazin-3(4H)-yl)methyl]-5-methoxy-4-methylphenyl}propanoate (1 eq.) as a reactant, the title compound (quant.) was obtained.

30 <sup>1</sup>H-NMR (400 MHz, DMSO-d<sub>6</sub>) δ ppm: 7.67 (d, 1 H), 7.45 (d, 1 H), 7.23 (s, 1 H), 6.98 (d, 1 H), 6.79 (dd, 1 H), 6.12 (d, 1 H), 5.81 (d, 1 H), 4.83-4.74 (m, 3 H), 4.16-3.78 (m, 6 H), 3.9 (s, 3 H), 3.64/3.4 (dt, 2 H), 3.21/3.07 (dd, 2 H), 2.64 (s, 3 H), 2.24-2.03 (m, 2 H), 2.14 (s, 3 H), 1.82/1.65 (m, 2 H), 1.02 (t, 3 H)

**STEP 6 : Preparation of EXAMPLE 30**

Using General Procedure 12 starting from ethyl [5-methoxy-4,31-dimethyl-27,27-dioxo-21,26-dioxa-27 $\lambda^6$ -thia-1,14,15,16-tetraazahexacyclo[20.5.3.1<sup>3,7</sup>.1<sup>9,13</sup>.0<sup>12,16</sup>.0<sup>25,29</sup>]dotriaconta-3(32),4,6,9(31),10,12,14,22,24,29-decaen-8-yl]acetate (1 eq.) as a reactant, the title compound (white solid, 66% yield) was obtained.

The enantiopure products were obtained by chromatographic separation on chiral column.

10 **Example 30a (E1)**

**HRMS** calculated for C<sub>30</sub>H<sub>32</sub>N<sub>4</sub>O<sub>7</sub>S: 592.1992; [M+H]<sup>+</sup> found: 593.2069 ( $\delta$ =0.8 ppm)

**Example 30b (E2)**

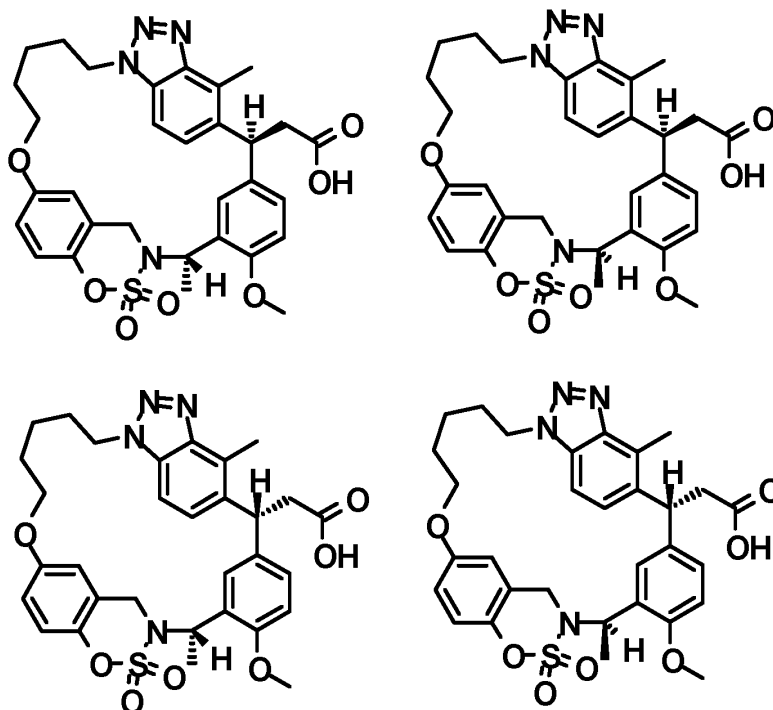
**HRMS** calculated for C<sub>30</sub>H<sub>32</sub>N<sub>4</sub>O<sub>7</sub>S: 592.1992; [M+H]<sup>+</sup> found: 593.2066 ( $\delta$ =0.3 ppm)

15 **<sup>1</sup>H-NMR** (400 MHz, DMSO-d<sub>6</sub>)  $\delta$  ppm: 12.2 (m, 1 H), 7.7 (d, 1 H), 7.45 (d, 1 H), 7.25 (d, 1 H), 7 (d, 1 H), 6.8 (dd, 1 H), 6.11 (d, 1 H), 5.8 (d, 1 H), 4.8 (m, 3 H), 4.12/3.82 (d, 2 H), 4.03/3.85 (d, 2 H), 3.9 (s, 3 H), 3.65/3.4 (m, 2 H), 3.1/2.98 (dd, 2 H), 2.62 (s, 3 H), 2.21/2.1 (m, 2 H), 2.18 (s, 3 H), 1.88/1.68 (m, 2 H)

20 **EXAMPLE 31** : [(2*S*,8*S*)-4-methoxy-2,32-dimethyl-28,28-dioxo-22,27-dioxa-28 $\lambda^6$ -thia-1,14,15,16-tetraazahexacyclo[21.5.3.1<sup>3,7</sup>.1<sup>9,13</sup>.0<sup>12,16</sup>.0<sup>26,30</sup>]tritiaconta-3(33),4,6,9(32),10,12,14,23,25,30-decaen-8-yl]acetic acid,  
[(2*R*,8*S*)-4-methoxy-2,32-dimethyl-28,28-dioxo-22,27-dioxa-28 $\lambda^6$ -thia-1,14,15,16-tetraazahexacyclo[21.5.3.1<sup>3,7</sup>.1<sup>9,13</sup>.0<sup>12,16</sup>.0<sup>26,30</sup>]tritiaconta-3(33),4,6,9(32),10,12,14,23,25,30-decaen-8-yl]acetic acid,  
25 [(2*S*,8*R*)-4-methoxy-2,32-dimethyl-28,28-dioxo-22,27-dioxa-28 $\lambda^6$ -thia-1,14,15,16-tetraazahexacyclo[21.5.3.1<sup>3,7</sup>.1<sup>9,13</sup>.0<sup>12,16</sup>.0<sup>26,30</sup>]tritiaconta-3(33),4,6,9(32),10,12,14,23,25,30-decaen-8-yl]acetic acid and

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[(2*R*,8*R*)-4-methoxy-2,32-dimethyl-28,28-dioxo-22,27-dioxa-28 $\lambda^6$ -thia-1,14,15,16-tetraazahexacyclo[21.5.3.1<sup>3,7</sup>.1<sup>9,13</sup>.0<sup>12,16</sup>.0<sup>26,30</sup>]tritiaconta-3(33),4,6,9(32),10,12,14,23,25,30-decaen-8-yl]acetic acid



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#### STEP A1 : Preparation of {[5-(iodopentyl)oxy]methyl}benzene

To a solution of 5-(benzyloxy)pentan-1-ol (1 eq., 1.15 kg, 5.92 mol) in DCM (8 L) PPh<sub>3</sub> (1.3 eq., 2.02 kg, 7.70 mol) and imidazole (1.3 eq., 524 g, 7.70 mol) were added at 15 °C. Iodine (1.3 eq., 1.95 kg, 7.70 mol) was added to the mixture at 0~15 °C by portions. The mixture was stirred at 15 °C for 0.5 h. After the completion of the reaction, the mixture was quenched with sat. aq. Na<sub>2</sub>SO<sub>3</sub> (5 L). The organic layer was separated, dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated under reduced pressure. The residue was cooled to 0°C slowly. The precipitate formed was filtered out, the filter cake was washed with MTBE (2x1.3 L) and the filtrate was concentrated under reduced pressure. The residue was purified by normal phase silica gel

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chromatography using petroleum ether / EtOAc 0 to 50: 1 eluent to give the title compound (pale yellow oil, 1.45 kg, 81% yield).

<sup>1</sup>H-NMR (400 MHz, CDCl<sub>3</sub>) δ ppm: 7.27-7.37 (m, 5H), 4.52 (m, 2H), 3.49 (t, *J* = 6.4 Hz, 2H), 3.20 (t, *J* = 7.2 Hz, 2H), 1.84-1.88 (m, 2H), 1.64- 1.67 (m, 2H), 1.49-1.53 (m, 2H)

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#### STEP A2 : Preparation of *N*-[5-(benzyloxy)pentyl]-4-bromo-3-methyl-2-nitroaniline

To a solution of 4-bromo-3-methyl-2-nitro-aniline (1 eq., 25 g, 108 mmol) and {[5-iodopentyl)oxy)methyl} benzene (1.5 eq., 49.4 g, 162 mmol) in DMF (250 mL) potassium tert-butylate was added portion-wise (1.5 eq., 18.2 g, 162 mmol) at 0-5°C, then the mixture was stirred at RT for 3 h. The reaction mixture was poured into H<sub>2</sub>O (520 mL), extracted with MTBE (3x90 mL). The combined organic layers were dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated to dryness. The residue was purified by normal phase silica gel chromatography using petroleum ether / EtOAc 0 to 7: 1 eluent to give the title compound (red oil, 26.46 g, 65 mmol, 60% yield).

<sup>1</sup>H-NMR (400 MHz, CDCl<sub>3</sub>) δ ppm: 7.46 (d, *J* = 9.2 Hz, 1H), 7.33-7.36 (m, 5H), 6.54 (d, *J* = 9.2 Hz, 1H), 5.72 (s, 1H), 4.51 (s, 2H), 3.49 (t, *J* = 6.4 Hz, 2H), 3.13-3.18 (m, 2H), 2.45 (s, 3H), 1.64-1.71 (m, 4H), 1.44-1.52 (m, 2H)

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#### STEP A3 : Preparation of *N*<sup>1</sup>-[5-(benzyloxy)pentyl]-4-bromo-3-methylbenzene-1,2-diamine

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To a solution of *N*-[5-(benzyloxy)pentyl]-4-bromo-3-methyl-2-nitroaniline (1 eq., 316 g, 776 mmol) in EtOH (1.9 L) and water (950 mL) NH<sub>4</sub>Cl (10 eq., 415 g, 7.76 mol) was added. The mixture was heated to 70 °C, then iron (5 eq., 217 g, 3.88 mol) was added in small portions and the mixture was heated at 80 °C for 1 h. The reaction mixture was cooled to 50 °C, bergmehl was added and the stirring was continued for 10 min. The reaction mixture was filtered through bergmehl. The filter cake was washed with hot EtOAc (2x2.5 L at 50 °C) and the filtrate was concentrated under reduced pressure. The aq. layer was extracted with EtOAc (3x1.3 L), the organic layer was washed with brine (3x0.5 L), dried over Na<sub>2</sub>SO<sub>4</sub> and concentrated under reduced pressure. To the crude product (250 g) petroleum ether: EtOAc 10:1 (750 mL) was

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added, the mixture was stirred at 25 °C for 16 h. The precipitate was filtered out and the filter cake was washed with petroleum ether: EtOAc 10:1 (100 mL), then dried in vacuo. The crude product (161 g, 427 mmol, 55% yield) was obtained as light brown solid.

**<sup>1</sup>H-NMR** (400 MHz, CDCl<sub>3</sub>) δ ppm: 7.27-7.36 (m, 5H), 7.01 (d, *J* = 8.8 Hz, 1H), 6.45 (d, *J* = 8.4 Hz, 1H), 4.52 (s, 2H), 3.47-3.52 (m, 4H), 3.08 (t, *J* = 6.8 Hz, 2H), 2.32 (s, 3H), 1.65-1.71 (m, 4H), 1.53-1.57 (m, 2H)

#### STEP A4 : Preparation of 1-[5-(benzyloxy)pentyl]-5-bromo-4-methyl-1*H*-benzotriazole

To a solution of *N*<sup>1</sup>-[5-(benzyloxy)pentyl]-4-bromo-3-methylbenzene-1,2-diamine (1 eq., 200 g, 530 mmol) in MeCN (1.40 L) 3-methylbutyl nitrite (2.5 eq., 155 g, 1.33 mol) was added at RT and the mixture was stirred for 16 h. After the reaction completed, the mixture was concentrated under reduced pressure. The residue was dissolved in EtOAc (1 L), washed with sat. Na<sub>2</sub>SO<sub>3</sub> (3x340 mL), then the organic layer was washed with brine (0.5 L). The aq. layer was extracted with EtOAc (2x170 mL), the combined organic layers were dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated under reduced pressure. The crude product was purified by normal phase silica gel chromatography using petroleum ether / EtOAc 0 to 50: 1 to give the title compound (134 g, 346.7 mmol, 65% yield) as black oil.

**<sup>1</sup>H-NMR** (400 MHz, CDCl<sub>3</sub>) δ ppm: 7.49 (d, *J* = 8.8 Hz, 1H), 7.20-7.26 (m, 5H), 7.12 (d, *J* = 8.8 Hz, 1H), 4.52 (t, *J* = 6.8 Hz, 2H), 4.39 (s, 2H), 3.36 (t, *J* = 6.4 Hz, 2H), 2.76 (s, 3H), 1.92-1.97 (m, 2H), 1.56-1.60 (m, 2H), 1.33-1.37 (m, 2H)

#### STEP A5 : Preparation of ethyl (2*E*)-3-{1-[5-(benzyloxy)pentyl]-4-methyl-1*H*-benzotriazol-5-yl}prop-2-enoate

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Using General Procedure 2 STEP 5 starting from 1-[5-(benzyloxy)pentyl]-5-bromo-4-methyl-1*H*-benzotriazole (1 eq.) as a reactant, the title compound (58% yield) was obtained.

**<sup>1</sup>H-NMR** (400 MHz, CDCl<sub>3</sub>) δ ppm: 8.14 (d, *J* = 16.4 Hz, 1H), 7.68 (d, *J* = 9.2 Hz, 1H), 7.23-7.40 (m, 5H), 6.42 (d, *J* = 15.6 Hz, 1H), 4.62 (t, *J* = 7.2 Hz, 2H), 4.40-4.53 (m, 2H), 4.31 (q, *J*



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= 7.2 Hz, 2H), 3.45 (t,  $J$  = 6.4 Hz, 2H), 2.92 (s, 3H), 2.03 (m, 2H), 1.62-1.76 (m, 2H), 1.40-1.50 (m, 2H), 1.37 (t,  $J$  = 7.2 Hz, 3H)

**STEP 1 : Preparation of ethyl 3-{1-[5-(benzyloxy)pentyl]-4-methyl-1*H*-benzotriazol-5-yl}-3-[3-(1-hydroxyethyl)-4-methoxyphenyl]propanoate**

Using General Procedure 6 starting from ethyl (2*E*)-3-{1-[5-(benzyloxy)pentyl]-4-methyl-1*H*-benzotriazol-5-yl}prop-2-enoate (1 eq.) and 1-[2-methoxy-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]ethan-1-ol (1.1 eq.) as reactants, the title compound (70% yield) was obtained.

<sup>1</sup>H-NMR (400 MHz, DMSO-d<sub>6</sub>) δ ppm: 7.61 (d, 1 H), 7.45 (d, 1 H), 7.38 (d, 1 H), 7.32-7.2 (m, 5 H), 7.12 (dd, 1 H), 6.81 (d, 1 H), 4.9 (d, 1 H), 4.9 (m, 1 H), 4.8 (m, 1 H), 4.61 (t, 2 H), 4.4 (s, 2 H), 3.91 (q, 2 H), 3.7 (s, 3 H), 3.38 (t, 2 H), 3.1 (d, 2 H), 2.78 (2s, 3 H), 1.89 (m, 2 H), 1.55 (m, 2 H), 1.3 (m, 2 H), 1.2 (2d, 3 H), 1 (t, 3 H)

**STEP 2 : Preparation of ethyl 3-(3-{1-[6-(benzyloxy)-2,2-dioxo-2*H*-1,2λ<sup>6</sup>,3-benzoxathiazin-3(4*H*)-yl]ethyl}-4-methoxyphenyl)-3-{1-[5-(benzyloxy)pentyl]-4-methyl-1*H*-benzotriazol-5-yl}propanoate**

Using General Procedure 7 starting from ethyl 3-{1-[5-(benzyloxy)pentyl]-4-methyl-1*H*-benzotriazol-5-yl}-3-[3-(1-hydroxyethyl)-4-methoxyphenyl]propanoate (1 eq.) and 6-(benzyloxy)-3,4-dihydro-2*H*-1,2λ<sup>6</sup>,3-benzoxathiazine-2,2-dione (1.1 eq.) as reactants, the title compound (58% yield) was obtained.

<sup>1</sup>H-NMR (400 MHz, DMSO-d<sub>6</sub>) δ ppm: 7.6 (d, 1 H), 7.5 (2d, 1 H), 7.45-7.2 (m, 11 H), 7.1 (2d, 1 H), 6.9 (m, 2 H), 6.75 (m, 2 H), 5.39 (m, 1 H), 5.02 (m, 2 H), 4.81 (m, 1 H), 4.6-4.5 (m, 2 H), 4.6 (2t, 2 H), 4.4 (s, 2 H), 3.91 (q, 2 H), 3.65 (s, 3 H), 3.35 (m, 2 H), 3.18 (d, 2 H), 2.78 (s, 3 H), 1.89 (m, 2 H), 1.55 (m, 2 H), 1.45 (2d, 3 H), 1.28 (m, 2 H), 0.99 (t, 3 H)

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**STEP 3 : Preparation of ethyl 3-{3-[1-(6-hydroxy-2,2-dioxo-2*H*-1,2λ<sup>6</sup>,3-benzoxathiazin-3(4*H*)-yl)ethyl]-4-methoxyphenyl}-3-[1-(5-hydroxypentyl)-4-methyl-1*H*-benzotriazol-5-yl]propanoate**

5 Using General Procedure 8 starting from ethyl 3-(3-{1-[6-(benzyloxy)-2,2-dioxo-2*H*-1,2λ<sup>6</sup>,3-benzoxathiazin-3(4*H*)-yl]ethyl}-4-methoxyphenyl)-3-{1-[5-(benzyloxy)pentyl]-4-methyl-1*H*-benzotriazol-5-yl}propanoate (1 eq.) as a reactant, the title compound (84% yield) was obtained. <sup>1</sup>H-NMR (400 MHz, DMSO-d<sub>6</sub>) δ ppm: 9.5/4.3 (s+m, 2 H), 7.62 (d, 1 H), 7.52 (d, 1 H), 7.41 (d, 1 H), 7.15 (dd, 1 H), 6.81 (d, 1 H), 6.79 (d, 1 H), 6.69 (dd, 1 H), 6.5 (d, 1 H), 5.39 (m, 1 H),  
10 4.81 (m, 1 H), 4.65 (t, 2 H), 4.6-4.4 (m, 2 H), 3.92 (q, 2 H), 3.68 (s, 3 H), 3.3 (m, 2 H), 3.2 (d, 2 H), 2.79 (2s, 3 H), 1.88 (m, 2 H), 1.45 (m, 5 H), 1.25 (m, 2 H), 1 (2t, 3 H)

**STEP 4 : Preparation of ethyl 3-[1-(5-bromopentyl)-4-methyl-1*H*-benzotriazol-5-yl]-3-{3-[1-(6-hydroxy-2,2-dioxo-2*H*-1,2λ<sup>6</sup>,3-benzoxathiazin-3(4*H*)-yl)ethyl]-4-methoxyphenyl}propanoate**

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Using General Procedure 9 starting from ethyl 3-{3-[1-(6-hydroxy-2,2-dioxo-2*H*-1,2λ<sup>6</sup>,3-benzoxathiazin-3(4*H*)-yl)ethyl]-4-methoxyphenyl}-3-[1-(5-hydroxypentyl)-4-methyl-1*H*-benzotriazol-5-yl]propanoate (1 eq.) as a reactant, the title compound (white solid, 66% yield)  
20 was obtained.

<sup>1</sup>H-NMR (400 MHz, DMSO-d<sub>6</sub>) δ ppm: 9.42 (s, 1 H), 7.65 (d, 1 H), 7.55 (d, 1 H), 7.41 (d, 1 H), 7.12 (dd, 1 H), 6.81 (d, 1 H), 6.79 (d, 1 H), 6.65 (dd, 1 H), 6.5 (d, 1 H), 5.39 (m, 1 H), 4.81 (m, 1 H), 4.65 (t, 2 H), 4.6-4.4 (m, 2 H), 3.92 (q, 2 H), 3.68 (s, 3 H), 3.49 (t, 2 H), 3.2 (d, 2 H), 2.79 (2s, 3 H), 1.9 (m, 2 H), 1.8 (m, 2 H), 1.45 (d, 3 H), 1.35 (m, 2 H), 1 (t, 3 H)

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**STEP 5 : Preparation of ethyl [4-methoxy-2,3,2-dimethyl-28,28-dioxo-22,27-dioxa-28λ<sup>6</sup>-thia-1,14,15,16-tetraazahexacyclo[21.5.3.1<sup>3,7</sup>.1<sup>9,13</sup>.0<sup>12,16</sup>.0<sup>26,30</sup>]tritiaconta-3(33),4,6,9(32),10,12,14,23,25,30-decaen-8-yl]acetate**

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Using General Procedure 11 starting from ethyl 3-[1-(5-bromopentyl)-4-methyl-1*H*-benzotriazol-5-yl]-3-{3-[1-(6-hydroxy-2,2-dioxo-2*H*-1,2λ<sup>6</sup>,3-benzoxathiazin-3(4*H*)-yl)ethyl]-4-methoxyphenyl}propanoate (1 eq.) as a reactant, the title compound (quant.) was obtained.

**<sup>1</sup>H-NMR** (400 MHz, DMSO-d<sub>6</sub>) δ ppm: 1.01 (t, J=7.03 Hz, 7 H) 1.25 (d, J=7.34 Hz, 4 H) 1.35 (d, J=4.89 Hz, 5 H) 1.50 (d, J=7.09 Hz, 5 H) 1.55 - 1.74 (m, 5 H) 1.88 - 1.97 (m, 3 H) 2.70 - 2.78 (m, 2 H) 2.81 (s, 3 H) 2.86 (s, 3 H) 3.01 (dd, J=15.53, 7.70 Hz, 1 H) 3.17 (ddd, J=15.62, 7.61, 4.16 Hz, 4 H) 3.62 (s, 4 H) 3.65 - 3.74 (m, 6 H) 3.76 - 3.84 (m, 1 H) 3.92 (quin, J=7.24 Hz, 4 H) 4.01 (d, J=2.32 Hz, 2 H) 4.14 (d, J=17.97 Hz, 1 H) 4.41 (d, J=17.61 Hz, 1 H) 4.70 (d, J=6.24 Hz, 4 H) 4.83 (t, J=8.13 Hz, 1 H) 4.89 (t, J=7.58 Hz, 1 H) 5.42 - 5.55 (m, 2 H) 5.69 (d, J=2.69 Hz, 1 H) 6.11 (d, J=2.81 Hz, 1 H) 6.66 - 6.77 (m, 4 H) 6.85 (dd, J=10.88, 9.05 Hz, 2 H) 6.94 (d, J=8.68 Hz, 1 H) 7.01 (d, J=1.96 Hz, 1 H) 7.15 - 7.20 (m, 1 H) 7.26 (d, J=8.80 Hz, 1 H) 7.47 - 7.54 (m, 2 H) 7.59 - 7.65 (m, 2 H) 7.66 - 7.73 (m, 2 H)

#### STEP 6 : Preparation of EXAMPLE 31

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Using General Procedure 12 starting from ethyl [4-methoxy-2,32-dimethyl-28,28-dioxo-22,27-dioxa-28λ<sup>6</sup>-thia-1,14,15,16-tetraazahexacyclo[21.5.3.1<sup>3,7</sup>.1<sup>9,13</sup>.0<sup>12,16</sup>.0<sup>26,30</sup>]tritiaconta-3(33),4,6,9(32),10,12,14,23,25,30-decaen-8-yl]acetate (1 eq.) as a reactant, the title compound (white solid, 67% yield) was obtained.

20 The diastereo-pure products were obtained by chromatographic separation on chiral column.

#### Example 31a (2*S*,8*S*)

**HRMS** calculated for C<sub>31</sub>H<sub>34</sub>N<sub>4</sub>O<sub>7</sub>S: 606.2148; [M+H]<sup>+</sup> found: 607.2223 (δ=0.3 ppm)

**<sup>1</sup>H-NMR** (400 MHz, DMSO-d<sub>6</sub>) δ ppm: 7.61 (d, 1 H), 7.51 (dd, 1 H), 7.21 (d, 1 H), 7 (d, 1 H), 6.99 (d, 1 H), 6.88 (d, 1 H), 6.75 (dd, 1 H), 5.75 (d, 1 H), 5.49 (q, 1 H), 4.9 (t, 1 H), 4.7 (m, 2 H), 4 (s, 2 H), 3.81/3.61 (2m, 2 H), 3.72 (s, 3 H), 3.09/2.88 (2dd, 2 H), 2.81 (s, 3 H), 2 (m, 2 H), 1.65 (m, 2 H), 1.38/1.18 (2m, 2 H), 1.28 (d, 3 H)

#### Example 31b (2*R*,8*S*)

30 **HRMS** calculated for C<sub>31</sub>H<sub>34</sub>N<sub>4</sub>O<sub>7</sub>S: 606.2148; [M+H]<sup>+</sup> found: 607.2221 (δ=0.0 ppm)

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**<sup>1</sup>H-NMR** (400 MHz, DMSO-d<sub>6</sub>) δ ppm: 7.7 (s, 2 H), 7.58 (d, 1 H), 7.2 (dd, 1 H), 6.82 (d, 1 H), 6.71 (d, 1 H), 6.7 (dd, 1 H), 6.1 (d, 1 H), 5.5 (q, 1 H), 4.81 (t, 1 H), 4.7 (t, 2 H), 4.39/4.1 (2d, 2 H), 3.7 (m, 2 H), 3.61 (s, 3 H), 3.15/3.05 (2dd, 2 H), 2.8 (s, 3 H), 2 (m, 2 H), 1.7/1.52 (2m, 2 H), 1.48 (d, 3 H), 1.39/1.18 (2m, 2 H)

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**Example 31c (2S,8R)**

**HRMS** calculated for C<sub>31</sub>H<sub>34</sub>N<sub>4</sub>O<sub>7</sub>S: 606.2148; [M+H]<sup>+</sup> found: 607.2232 (δ=1.8 ppm)

**<sup>1</sup>H-NMR** (400 MHz, DMSO-d<sub>6</sub>) δ ppm: 12.07 (sl, 1 H), 7.68 (s, 2 H), 7.46 (d, 1 H), 7.19 (dd, 1 H), 6.84 (d, 1 H), 6.73 (d, 1 H), 6.71 (dd, 1 H), 6.09 (d, 1 H), 5.5 (q, 1 H), 4.81 (t, 1 H), 4.7 (t, 2 H), 4.38/4.1 (2d, 2 H), 3.71 (m, 2 H), 3.63 (s, 3 H), 3.15/3.05 (2dd, 2 H), 2.8 (s, 3 H), 1.99 (m, 2 H), 1.69/1.53 (2m, 2 H), 1.47 (d, 3 H), 1.38/1.18 (2m, 2 H)

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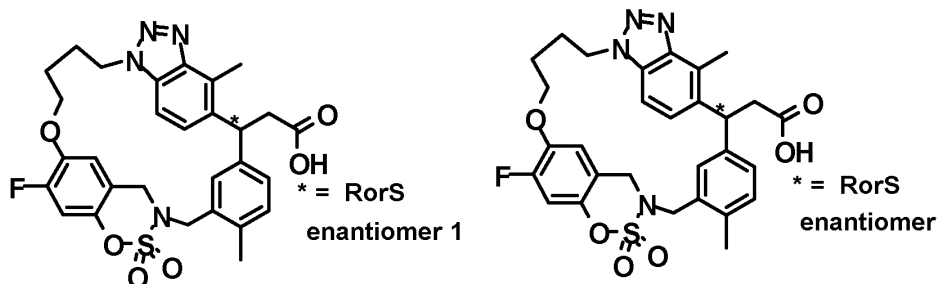
**Example 31d (2R,8R)**

**HRMS** calculated for C<sub>31</sub>H<sub>34</sub>N<sub>4</sub>O<sub>7</sub>S: 606.2148; [M+H]<sup>+</sup> found: 607.2221 (δ=0.0 ppm)

**<sup>1</sup>H-NMR** (400 MHz, DMSO-d<sub>6</sub>) δ ppm: 12.2 (sl, 1 H), 7.61 (d, 1 H), 7.53 (dd, 1 H), 7.2 (d, 1 H), 6.99/6.97 (2d, 2 H), 6.87 (d, 1 H), 6.75 (dd, 1 H), 5.74 (d, 1 H), 5.46 (q, 1 H), 4.88 (t, 1 H), 4.69 (m, 2 H), 3.99 (s, 2 H), 3.82/3.63 (2m, 2 H), 3.74 (s, 3 H), 3.07/2.87 (dd+m, 2 H), 2.85 (s, 3 H), 1.99 (m, 2 H), 1.63 (m, 2 H), 1.37/1.18 (2m, 2 H), 1.24 (d, 3 H)

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20 **EXAMPLE 32** : [23-Fluoro-4,31-dimethyl-27,27-dioxo-21,26-dioxa-27λ<sup>6</sup>-thia-1,14,15,16-tetraazahexacyclo[20.5.3.1<sup>3,7</sup>.1<sup>9,13</sup>.0<sup>12,16</sup>.0<sup>25,29</sup>]dotriaconta-3(32),4,6,9(31),10,12,14,22,24,29-decaen-8-yl]acetic acid



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**STEP C1 : Preparation of 5-(benzyloxy)-4-fluoro-2-hydroxybenzaldehyde**

Using General Procedure 4 STEP 1 starting from 4-(benzyloxy)-3-fluorophenol (1 eq.) as a reactant, the title compound (95% yield) was obtained.

- 5 <sup>1</sup>H-NMR (500 MHz, DMSO-d<sub>6</sub>) δ ppm: 10.78 (s, 1 H), 10.18 (s, 1 H), 7.48-7.29 (m, 5 H), 7.43 (d, 1 H), 6.87 (d, 1 H), 5.13 (s, 2 H)

**STEP C2 : Preparation of 6-(benzyloxy)-7-fluoro-2*H*-1,2λ<sup>6</sup>,3-benzoxathiazine-2,2-dione**

- 10 Using General Procedure 4 STEP 2 starting from 5-(benzyloxy)-4-fluoro-2-hydroxybenzaldehyde (1 eq.) as a reactant, the title compound (94% yield) was obtained.  
<sup>1</sup>H-NMR (500 MHz, DMSO-d<sub>6</sub>) δ ppm: 9.11 (s, 1 H), 7.97 (d, 1 H), 7.76 (d, 1 H), 7.52-7.36 (m, 5 H), 5.25 (s, 2 H)

- 15 **STEP C3 : Preparation of 6-(benzyloxy)-7-fluoro-3,4-dihydro-2*H*-1,2λ<sup>6</sup>,3-benzoxathiazine-2,2-dione**

- Using General Procedure 4 STEP 3 starting from 6-(benzyloxy)-7-fluoro-2*H*-1,2λ<sup>6</sup>,3-benzoxathiazine-2,2-dione (1 eq.) as a reactant, the title compound (yellow solid, 86% yield)  
20 was obtained.  
<sup>1</sup>H-NMR (500 MHz, DMSO-d<sub>6</sub>) δ ppm: 8.56 (brs, 1 H), 7.48-7.32 (m, 5 H), 7.25 (d, 1 H), 7.19 (d, 1 H), 5.14 (s, 2 H), 4.5 (s, 2 H)

- STEP 1 : Preparation of ethyl 3-{1-[4-(benzyloxy)butyl]-4-methyl-1*H*-benzotriazol-5-yl}-3-(3-{[6-(benzyloxy)-7-fluoro-2,2-dioxo-2*H*-1,2λ<sup>6</sup>,3-benzoxathiazin-3(4*H*)-yl]methyl}-4-methylphenyl)propanoate**  
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- Using General Procedure 7 starting from ethyl (2*E*)-3-{1-[4-(benzyloxy)butyl]-4-methyl-1*H*-benzotriazol-5-yl}prop-2-enoate (1 eq.) and 6-(benzyloxy)-7-fluoro-3,4-dihydro-2*H*-1,2λ<sup>6</sup>,3-benzoxathiazine-2,2-dione (1.2 eq.) as reactants, the title compound (66% yield) was obtained.  
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<sup>1</sup>H-NMR (500 MHz, DMSO-d<sub>6</sub>) δ ppm: 7.58 (d, 1 H), 7.49 (d, 1 H), 7.47 (dm, 2 H), 7.41 (tm, 2 H), 7.36 (tm, 1 H), 7.3 (d, 1 H), 7.3 (m, 2 H), 7.27 (d, 1 H), 7.25 (m, 2 H), 7.25 (d, 1 H), 7.24 (m, 1 H), 7.2 (dd, 1 H), 7.13 (d, 1 H), 5.14 (s, 2 H), 4.86 (t, 1 H), 4.64 (t, 2 H), 4.47/4.42 (d+d, 2 H), 4.38 (s, 2 H), 4.26/4.21 (d+d, 2 H), 3.92 (q, 2 H), 3.39 (t, 2 H), 3.2/3.16 (dd+dd, 2 H),  
5 2.77 (s, 3 H), 2.2 (s, 3 H), 1.92 (m, 2 H), 1.47 (m, 2 H), 0.97 (t, 3 H)

**STEP 2 : Preparation of ethyl 3-{3-[(7-fluoro-6-hydroxy-2,2-dioxo-2*H*-1,2λ<sup>6</sup>,3-benzoxathiazin-3(4*H*)-yl)methyl]-4-methylphenyl}-3-[1-(4-hydroxybutyl)-4-methyl-1*H*-benzotriazol-5-yl]propanoate**

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Using General Procedure 8 starting from ethyl 3-{1-[4-(benzyloxy)butyl]-4-methyl-1*H*-benzotriazol-5-yl}-3-(3-{[6-(benzyloxy)-7-fluoro-2,2-dioxo-2*H*-1,2λ<sup>6</sup>,3-benzoxathiazin-3(4*H*)-yl]methyl}-4-methylphenyl)propanoate (1 eq.) as a reactant, the title compound (white solid foam, 95% yield) was obtained.

15 <sup>1</sup>H-NMR (500 MHz, DMSO-d<sub>6</sub>) δ ppm: 10.17 (s, 1 H), 7.62 (d, 1 H), 7.52 (d, 1 H), 7.26 (d, 1 H), 7.2 (dd, 1 H), 7.18 (d, 1 H), 7.14 (d, 1 H), 6.84 (d, 1 H), 4.84 (t, 1 H), 4.65 (t, 2 H), 4.44 (brt., 1 H), 4.4 (s, 2 H), 4.25/4.2 (d+d, 2 H), 3.94 (q, 2 H), 3.38 (m, 2 H), 3.18 (d, 2 H), 2.77 (s, 3 H), 2.22 (s, 3 H), 1.9 (m, 2 H), 1.36 (m, 2 H), 1 (t, 3 H)

20 **STEP 3 : Preparation of ethyl 3-[1-(4-chlorobutyl)-4-methyl-benzotriazol-5-yl]-3-[3-[(7-fluoro-6-hydroxy-2,2-dioxo-4*H*-1,2λ<sup>6</sup>,3-benzoxathiazin-3-yl)methyl]-4-methyl-phenyl]propanoate**

Using General Procedure 10 starting from ethyl 3-{3-[(7-fluoro-6-hydroxy-2,2-dioxo-2*H*-1,2λ<sup>6</sup>,3-benzoxathiazin-3(4*H*)-yl)methyl]-4-methylphenyl}-3-[1-(4-hydroxybutyl)-4-methyl-1*H*-benzotriazol-5-yl]propanoate (1 eq.) as a reactant, the title compound (yellow oil, quant.)  
25 was obtained.

<sup>1</sup>H-NMR (500 MHz, DMSO-d<sub>6</sub>) δ ppm: 10.17 (s, 1 H), 7.64 (d, 1 H), 7.53 (d, 1 H), 7.25 (d, 1 H), 7.2 (dd, 1 H), 7.18 (d, 1 H), 7.14 (d, 1 H), 6.84 (d, 1 H), 4.85 (t, 1 H), 4.7 (t, 2 H), 4.4 (s, 2

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H), 4.25/4.19 (d+d, 2 H), 3.94 (q, 2 H), 3.65 (t, 2 H), 3.18 (d, 2 H), 2.77 (s, 3 H), 2.22 (s, 3 H), 1.99 (m, 2 H), 1.68 (m, 2 H), 1 (t, 3 H)

5                   **STEP 4 : Preparation of ethyl [23-fluoro-4,31-dimethyl-27,27-dioxo-21,26-dioxa-27 $\lambda$ -  
thia-1,14,15,16-tetraazahexacyclo[20.5.3.1<sup>3,7</sup>.1<sup>9,13</sup>.0<sup>12,16</sup>.0<sup>25,29</sup>]dotriaconta-  
3(32),4,6,9(31),10,12,14,22,24,29-decaen-8-yl]acetate**

10                   Using General Procedure 11 starting from ethyl 3-[1-(4-chlorobutyl)-4-methyl-benzotriazol-5-  
yl]-3-[3-[(7-fluoro-6-hydroxy-2,2-dioxo-4H-1,2 $\lambda$ 6,3-benzoxathiazin-3-yl)methyl]-4-methyl-  
phenyl]propanoate (1 eq.) as a reactant, the title compound (white solid foam, 69% yield) was  
obtained.

15                   <sup>1</sup>H-NMR (500 MHz, DMSO-d<sub>6</sub>)  $\delta$  ppm: 7.69 (d, 1 H), 7.47 (dd, 1 H), 7.47 (d, 1 H), 7.27 (d, 1  
H), 7.2 (d, 1 H), 6.64 (d, 1 H), 6.1 (d, 1 H), 4.83/4.76 (m+m, 2 H), 4.78 (t, 1 H), 4.24/3.9 (d+d,  
2 H), 3.99/3.76 (d+d, 2 H), 3.92 (q, 2 H), 3.7/3.42 (m+m, 2 H), 3.14/3.06 (dd+dd, 2 H), 2.64  
(s, 3 H), 2.32 (s, 3 H), 2.21/2.01 (m+m, 2 H), 1.8/1.62 (m+m, 2 H), 1.01 (t, 3 H)

**STEP 5 : Preparation of EXAMPLE 32**

20                   Using General Procedure 12 starting from ethyl [23-fluoro-4,31-dimethyl-27,27-dioxo-21,26-  
dioxo-27 $\lambda$ -thia-1,14,15,16-tetraazahexacyclo[20.5.3.1<sup>3,7</sup>.1<sup>9,13</sup>.0<sup>12,16</sup>.0<sup>25,29</sup>]dotriaconta-  
3(32),4,6,9(31),10,12,14,22,24,29-decaen-8-yl]acetate (1 eq.) as a reactant, the title compound  
(white solid, 55% yield) was obtained.

The enantiopure products were obtained by chromatographic separation on chiral column.

25                   **Example 32a (E1)**

**HRMS** calculated for C<sub>29</sub>H<sub>29</sub>FN<sub>4</sub>O<sub>6</sub>S: 580.1792; [M+H]<sup>+</sup> found: 581.1863 ( $\delta$  = -0.3 ppm)

**Example 32b (E2)**

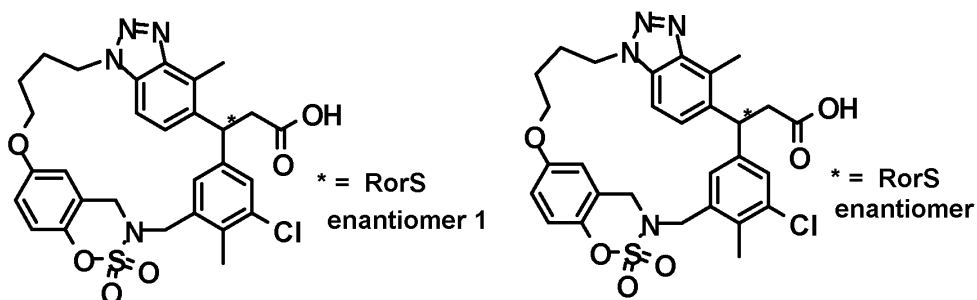
**HRMS** calculated for C<sub>29</sub>H<sub>29</sub>FN<sub>4</sub>O<sub>6</sub>S: 580.1792; [M+H]<sup>+</sup> found: 581.1867 ( $\delta$  = 0.4 ppm)

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**<sup>1</sup>H-NMR** (500 MHz, DMSO-d<sub>6</sub>) δ ppm: 7.68 (d, 1 H), 7.48 (s, 1 H), 7.45 (d, 1 H), 7.27 (s, 1 H), 7.2 (d, 1 H), 6.61 (s, 1 H), 6.08 (d, 1 H), 4.84/4.74 (m+m, 2 H), 4.75 (t, 1 H), 4.23/3.91 (d+d, 2 H), 3.99/3.76 (d+d, 2 H), 3.69/3.4 (m+m, 2 H), 3.01/2.94 (dd+dd, 2 H), 2.63 (s, 3 H), 2.31 (s, 3 H), 2.22/2.01 (m+m, 2 H), 1.81/1.62 (m+m, 2 H)

**<sup>13</sup>C-NMR** (125 MHz, DMSO-d<sub>6</sub>) δ ppm: 131.3, 131.3, 128.8, 127.2, 112.6, 107.9, 107.4, 68.7, 52, 48.5, 48.2, 41.9, 41.1, 26.8, 25.4, 16.5, 13.4

**EXAMPLE 33 :** [5-Chloro-4,31-dimethyl-27,27-dioxo-21,26-dioxa-27λ<sup>6</sup>-thia-1,14,15,16-tetraazahexacyclo[20.5.3.1<sup>3,7</sup>.1<sup>9,13</sup>.0<sup>12,16</sup>.0<sup>25,29</sup>]dotriaconta-3(32),4,6,9(31),10,12,14,22,24,29-decaen-8-yl]acetic acid



#### STEP B1 : Preparation of (5-bromo-3-chloro-2-methylphenyl)methanol

Methyl 5-bromo-3-chloro-2-methyl-benzoate (1 eq., 20.0 g, 75.9 mmol) was dissolved in EtOH (500mL), then sodium borohydride (3 eq., 8.6 g, 227.7mmol) was added to the stirred mixture at 0 °C. The mixture was stirred at this temperature for 10 min and calcium chloride (3 eq., 25.3 g, 227.7mmol) was added over a period of 30min. Then it was allowed to warm to RT and stirred at RT for 2h. The reaction mixture was quenched with cold 1M aq. HCl solution, extracted with EtOAc, the organic phase was separated, dried over MgSO<sub>4</sub>, concentrated under reduced pressure to give the crude product (17.0 g, 95% yield) as white solid, which was used in the next step without further purification.

**<sup>1</sup>H-NMR** (400 MHz, DMSO-d<sub>6</sub>) δ ppm: 7.58 (s, 1 H), 7.53 (s, 1 H), 5.42 (t, 1H), 4.52 (d, 2 H), 2.21 (s, 3 H)



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**STEP B2 : Preparation of [3-chloro-2-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]methanol**

- 5 Using General Procedure 3 starting from (5-bromo-3-chloro-2-methylphenyl)methanol (1 eq., 20.0 g., 84.9 mmol) as a reactant, gave the title compound (11.6 g, 48% yield).  
<sup>1</sup>H-NMR (400 MHz, DMSO-d<sub>6</sub>) δ ppm: 7.68 (d, 1 H), 7.5 (d, 1 H), 5.25 (t, 1 H), 4.52 (d, 2 H), 2.3 (s, 3 H), 1.3 (s, 12 H)

10 **STEP 1 : Preparation of ethyl 3-{1-[4-(benzyloxy)butyl]-4-methyl-1H-benzotriazol-5-yl}-3-[3-chloro-5-(hydroxymethyl)-4-methylphenyl]propanoate**

- Using General Procedure 6 starting from ethyl (2E)-3-{1-[4-(benzyloxy)butyl]-4-methyl-1H-benzotriazol-5-yl}prop-2-enoate (1 eq.) and [3-chloro-2-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]methanol (1.1 eq.) as reactants, the title compound (98% yield) was obtained.

<sup>1</sup>H-NMR (400 MHz, DMSO-d<sub>6</sub>) δ ppm: 7.6 (d, 1 H), 7.49 (d, 1 H), 7.29 (m, 7 H), 5.16 (t, 1 H), 4.84 (t, 1 H), 4.66 (t, 2 H), 4.44 (d, 2 H), 4.4 (s, 2 H), 3.94 (q, 2 H), 3.42 (t, 2 H), 3.16 (t, 2 H), 2.76 (s, 3 H), 2.19 (s, 3 H), 1.95 (quint, 2 H), 1.5 (quint, 2 H), 1 (t, 3 H)

20

**STEP 2 : Preparation of ethyl 3-{1-[4-(benzyloxy)butyl]-4-methyl-1H-benzotriazol-5-yl}-3-(3-{[6-(benzyloxy)-2,2-dioxo-2H-1,2λ<sup>6</sup>,3-benzoxathiazin-3(4H)-yl]methyl}-5-chloro-4-methylphenyl)propanoate**

- 25 Using General Procedure 7 starting from ethyl 3-{1-[4-(benzyloxy)butyl]-4-methyl-1H-benzotriazol-5-yl}-3-[3-chloro-5-(hydroxymethyl)-4-methylphenyl]propanoate (1 eq.) and 6-(benzyloxy)-3,4-dihydro-2H-1,2λ<sup>6</sup>,3-benzoxathiazine-2,2-dione (1.1 eq.) as reactants, the title compound (85% yield) was obtained.

- <sup>1</sup>H-NMR (400 MHz, DMSO-d<sub>6</sub>) δ ppm: 7.6 (d, 1 H), 7.51 (d, 1 H), 7.46 (d, 2 H), 7.42-7.22 (m, 10 H), 7.13 (d, 1 H), 7.06 (dd, 1 H), 6.93 (d, 1 H), 5.1 (s, 2 H), 4.85 (t, 1 H), 4.63 (t, 2 H), 4.44

30

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(sl, 2 H), 4.38 (s, 2 H), 4.29 (sl, 2 H), 3.93 (q, 2 H), 3.4 (t, 2 H), 3.2 (m, 2 H), 2.76 (s, 3 H), 2.26 (s, 3 H), 1.92 (quint, 2 H), 1.48 (quint, 2 H), 0.99 (t, 3 H)

**STEP 3 : Preparation of ethyl 3-{3-chloro-5-[(6-hydroxy-2,2-dioxo-2*H*-1,2λ<sup>6</sup>,3-benzoxathiazin-3(4*H*)-yl)methyl]-4-methylphenyl}-3-[1-(4-hydroxybutyl)-4-methyl-1*H*-benzotriazol-5-yl]propanoate**

Using General Procedure 8 starting from ethyl 3-{1-[4-(benzyloxy)butyl]-4-methyl-1*H*-benzotriazol-5-yl}-3-(3-{[6-(benzyloxy)-2,2-dioxo-2*H*-1,2λ<sup>6</sup>,3-benzoxathiazin-3(4*H*)-yl]methyl}-5-chloro-4-methylphenyl)propanoate (1 eq.) as a reactant, the title compound (white solid, 81% yield) was obtained.

**<sup>1</sup>H-NMR** (400 MHz, DMSO-d<sub>6</sub>) δ ppm: 9.7/4.41 (s+t, 2 H), 7.65 (d, 1 H), 7.55 (d, 1 H), 7.4/7.28 (2d, 2 H), 7 (d, 1 H), 6.8 (dd, 1 H), 6.6 (d, 1 H), 4.85 (t, 1 H), 4.65 (t, 2 H), 4.41 (s, 2 H), 4.28 (d, 2 H), 3.95 (q, 2 H), 3.38 (q, 2 H), 3.2 (m, 2 H), 2.78 (s, 3 H), 2.29 (s, 3 H), 1.9 (m, 2 H), 1.39 (m, 2 H), 1.02 (t, 3 H)

**STEP 4 : Preparation of ethyl 3-[1-(4-bromobutyl)-4-methyl-1*H*-benzotriazol-5-yl]-3-{3-chloro-5-[(6-hydroxy-2,2-dioxo-2*H*-1,2λ<sup>6</sup>,3-benzoxathiazin-3(4*H*)-yl)methyl]-4-methylphenyl}propanoate**

20

Using General Procedure 9 starting from ethyl 3-{3-chloro-5-[(6-hydroxy-2,2-dioxo-2*H*-1,2λ<sup>6</sup>,3-benzoxathiazin-3(4*H*)-yl)methyl]-4-methylphenyl}-3-[1-(4-hydroxybutyl)-4-methyl-1*H*-benzotriazol-5-yl]propanoate (1 eq.) as a reactant, the title compound (white solid, 74% yield) was obtained.

**<sup>1</sup>H-NMR** (400 MHz, DMSO-d<sub>6</sub>) δ ppm: 9.68 (s, 1 H), 7.65/7.55 (2d, 2 H), 7.39/7.26 (2d, 2 H), 6.99 (d, 1 H), 6.78 (dd, 1 H), 6.6 (d, 1 H), 4.84 (t, 1 H), 4.69 (t, 2 H), 4.4 (s, 2 H), 4.27 (d, 2 H), 3.95 (q, 2 H), 3.54 (t, 2 H), 3.2 (t, 2 H), 2.76 (s, 3 H), 2.26 (s, 3 H), 2 (m, 2 H), 1.78 (m, 2 H), 1.01 (t, 3 H)

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**STEP 5 : Preparation of ethyl [5-chloro-4,31-dimethyl-27,27-dioxo-21,26-dioxa-27 $\lambda$ <sup>6</sup>-thia-1,14,15,16-tetraazahexacyclo[20.5.3.1<sup>3,7</sup>.1<sup>9,13</sup>.0<sup>12,16</sup>.0<sup>25,29</sup>]dotriaconta-3(32),4,6,9(31),10,12,14,22,24,29-decaen-8-yl]acetate**

5 Using General Procedure 11 starting from ethyl 3-[1-(4-bromobutyl)-4-methyl-1*H*-benzotriazol-5-yl]-3-{3-chloro-5-[(6-hydroxy-2,2-dioxo-2*H*-1,2 $\lambda$ <sup>6</sup>,3-benzoxathiazin-3(4*H*)-yl)methyl]-4-methylphenyl}propanoate (1 eq.) as a reactant, the title compound (white solid, 45% yield) was obtained.

<sup>1</sup>H-NMR (400 MHz, DMSO-d<sub>6</sub>)  $\delta$  ppm: 7.68/5.88 (m+d, 2 H), 7.67/7.43 (2d, 2 H), 6.99 (d, 1  
10 H), 6.79 (dd, 1 H), 6.6 (d, 1 H), 4.82-4.73 (m, 1 H), 4.79 (t, 2 H), 4.19/4.04 (2d, 2 H),  
3.97/3.86 (2d, 2 H), 3.94 (m, 2 H), 3.67/3.45 (m+dt, 2 H), 3.21/3.06 (2dd, 2 H), 2.65 (s, 3 H),  
2.35 (s, 3 H), 2.21/2.06 (2m, 2 H), 1.8/1.6 (2m, 2 H), 1.02 (t, 3 H)

**STEP 6 : Preparation of EXAMPLE 33**

15

Using General Procedure 12 starting from ethyl [5-chloro-4,31-dimethyl-27,27-dioxo-21,26-dioxa-27 $\lambda$ <sup>6</sup>-thia-1,14,15,16-tetraazahexacyclo[20.5.3.1<sup>3,7</sup>.1<sup>9,13</sup>.0<sup>12,16</sup>.0<sup>25,29</sup>]dotriaconta-3(32),4,6,9(31),10,12,14,22,24,29-decaen-8-yl]acetate (1 eq.) as a reactant, the title compound (white solid, 90% yield) was obtained.

20 The enantiopure products were obtained by chromatographic separation on chiral column.

**Example 33a (E1)**

HRMS calculated for C<sub>29</sub>H<sub>29</sub>ClN<sub>4</sub>O<sub>6</sub>S: 596.1496; [M+H]<sup>+</sup> found: 597.1573 ( $\delta$ =0.7 ppm)

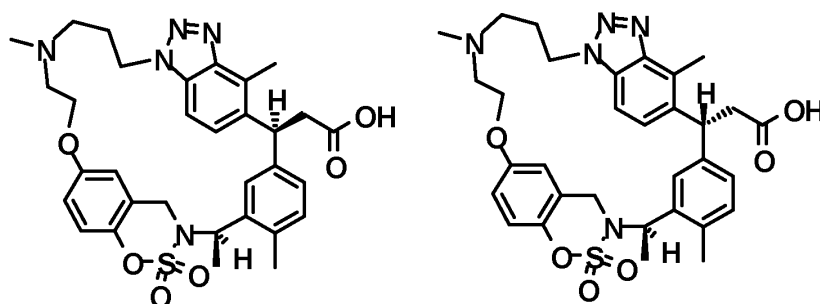
25 **Example 33b (E2)**

HRMS calculated for C<sub>29</sub>H<sub>29</sub>ClN<sub>4</sub>O<sub>6</sub>S: 596.1496; [M+H]<sup>+</sup> found: 597.1571 ( $\delta$ =0.3 ppm)

<sup>1</sup>H-NMR (400 MHz, DMSO-d<sub>6</sub>)  $\delta$  ppm: 12.27 (s, 1 H), 7.68 (s, 1 H), 7.67 (d, 1 H), 7.42 (d, 1  
H), 6.99 (d, 1 H), 6.79 (dd, 1 H), 6.58 (s, 1 H), 5.86 (d, 1 H), 4.82-4.72 (m, 3 H), 4.18/4.04 (2d,  
2 H), 3.98/3.85 (d, 2 H), 3.66/3.44 (m+dt, 2 H), 3.09/2.94 (2dd, 2 H), 2.64 (s, 3 H), 2.35 (s, 3  
30 H), 2.21/2.06 (2m, 2 H), 1.81/1.61 (2m, 2 H);

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**EXAMPLE 34 :** [(2*R*,8*S*)-2,4,20,33-tetramethyl-29,29-dioxo-23,28-dioxa-29 $\lambda^6$ -thia-  
 1,14,15,16,20-  
 pentaazahexacyclo[22.5.3.1<sup>3,7</sup>.1<sup>9,13</sup>.0<sup>12,16</sup>.0<sup>27,31</sup>]tetratriaconta-  
 3(34),4,6,9(33),10,12,14,24,26,31-decaen-8-yl]acetic acid and  
 [(2*R*,8*R*)-2,4,20,33-tetramethyl-29,29-dioxo-23,28-dioxa-29 $\lambda^6$ -thia-  
 1,14,15,16,20-  
 pentaazahexacyclo[22.5.3.1<sup>3,7</sup>.1<sup>9,13</sup>.0<sup>12,16</sup>.0<sup>27,31</sup>]tetratriaconta-  
 3(34),4,6,9(33),10,12,14,24,26,31-decaen-8-yl]acetic acid



**STEP A1 : Preparation of *tert*-butyl (3-{[2-(benzyloxy)ethyl](methyl)amino}propyl) carbamate**

To a solution of [(2-bromoethoxy)methyl]benzene (10 g, 46.5 mmol, 7.35 mL) in MeCN (3 mL/mmol, 139 mL) *tert*-butyl [3-(methylamino)propyl]carbamate (1 eq., 8.75 g, 46.5 mmol) and  $K_2CO_3$  (2 eq., 9.22 g, 93 mmol) were added at RT. The reaction mixture was heated to 50 °C and stirred for 2 h. After completion of the reaction the mixture was diluted with 500 ml of EtOAc, washed with 500 ml of water then with 500 ml of brine. The organic layer was dried over anhydrous  $Na_2SO_4$ , filtered, concentrated to dryness to give the crude product as a colorless oil, which was used in a next step without further purification (14.5 g, 77% yield).

$^1H$ -NMR (400 MHz, DMSO- $d_6$ )  $\delta$  ppm: 7.38-7.25 (m, 5 H), 6.74 (t, 1 H), 4.46 (s, 2 H), 3.5 (t, 2 H), 2.92 (q, 2 H), 2.5 (m, 2 H), 2.31 (t, 2 H), 2.15 (s, 3 H), 1.49 (quint, 2 H), 1.37 (s, 9 H)

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**STEP A2 : Preparation of  $N^1$ -[2-(benzyloxy)ethyl]- $N^1$ -methyl- $N^3$ -(3-methyl-2-nitrophenyl)propane-1,3-diamine**

5 To a solution of *tert*-butyl (3-{[2-(benzyloxy)ethyl](methyl)amino}propyl)carbamate (14.5 g, 36 mmol) in dioxane (5 mL/mmol, 180 mL) HCl (4N in dioxane) (4 eq., 36 mL) was added at RT. The reaction mixture was stirred overnight at RT. After completion of the reaction the solvent was evaporated to dryness under reduced pressure. The crude  $N^1$ -[2-(benzyloxy)ethyl]- $N^1$ -methylpropane-1,3-diamine hydrochloride (13.3 g, 68% yield) was reacted without further  
10 purification with 1-fluoro-3-methyl-2-nitrobenzene using General Procedure 2 STEP 1, resulting the title compound (78% yield).

**$^1\text{H-NMR}$**  (400 MHz, DMSO- $d_6$ )  $\delta$  ppm: 7.39-7.28 (m, 5 H), 7.25 (dd, 1 H), 6.78 (d, 1 H), 6.58 (d, 1 H), 6.55 (m, 1 H), 4.5 (s, 2 H), 3.67 (t, 2 H), 3.22 (q, 2 H), 2.98 (m, 2 H), 2.82 (quint, 2 H), 2.82 (m, 2 H), 2.5 (-, 3 H), 2.29 (s, 3 H)

15

**STEP A3 : Preparation of  $N^1$ -[2-(benzyloxy)ethyl]- $N^3$ -(4-bromo-3-methyl-2-nitrophenyl)- $N^1$ -methylpropane-1,3-diamine**

Using General Procedure 2 STEP 2 starting from  $N^1$ -[2-(benzyloxy)ethyl]- $N^1$ -methyl- $N^3$ -(3-methyl-2-nitrophenyl)propane-1,3-diamine (1 eq.) as a reactant, the title compound (65%  
20 yield) was obtained.

**$^1\text{H-NMR}$**  (400 MHz, DMSO- $d_6$ )  $\delta$  ppm: 7.5 (d, 1 H), 7.3 (m, 5 H), 6.7 (d, 1 H), 6.55 (t, 1 H), 4.45 (s, 2 H), 3.52 (t, 2 H), 3.15 (q, 2 H), 2.55 (t, 2 H), 2.45 (t, 2 H), 2.22/2.2 (2s, 6 H), 1.69 (m, 2 H)

25

**STEP A4 : Preparation of  $N$ -[2-(benzyloxy)ethyl]-3-(5-bromo-4-methyl-1*H*-benzotriazol-1-yl)- $N$ -methylpropan-1-amine**

Using General Procedure 2 STEP 3 starting from  $N^1$ -[2-(benzyloxy)ethyl]- $N^3$ -(4-bromo-3-methyl-2-nitrophenyl)- $N^1$ -methylpropane-1,3-diamine (1 eq.) as a reactant,  $N^1$ -(3-{[2-  
30 methyl-2-nitrophenyl)- $N^1$ -methylpropane-1,3-diamine (1 eq.) as a reactant,  $N^1$ -(3-{[2-

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(benzyloxy)ethyl](methyl)amino}propyl)-4-bromo-3-methylbenzene-1,2-diamine (76% yield) was obtained. The crude product was reacted using General Procedure 2 STEP 4 resulting the title compound (quant.).

**<sup>1</sup>H-NMR** (400 MHz, DMSO-d<sub>6</sub>) δ ppm: 7.63 (m, 2 H), 7.3 (m, 5 H), 4.7 (t, 2 H), 4.42 (s, 2 H), 3.48 (t, 2 H), 2.71 (s, 3 H), 2.49 (t, 2 H), 2.3 (t, 2 H), 2.15 (s, 3 H), 2.04 (q, 2 H)

**STEP A5 : Preparation of ethyl (2E)-3-[1-(3-{[2-(benzyloxy)ethyl](methyl)amino}propyl)-4-methyl-1H-benzotriazol-5-yl]prop-2-enoate**

Using General Procedure 2 STEP 5 starting from *N*-[2-(benzyloxy)ethyl]-3-(5-bromo-4-methyl-1H-benzotriazol-1-yl)-*N*-methylpropan-1-amine (1 eq.) as a reactant, the title compound (92% yield) was obtained.

**<sup>1</sup>H-NMR** (400 MHz, DMSO-d<sub>6</sub>) δ ppm: 8.02 (d, 1 H), 7.92/7.69 (dd, 2 H), 7.36-7.23 (m, 5 H), 6.62 (d, 1 H), 4.7 (t, 2 H), 4.42 (s, 2 H), 4.22 (q, 2 H), 3.48 (t, 2 H), 2.8 (s, 3 H), 2.5 (m, 2 H), 2.32 (t, 2 H), 2.16 (s, 3 H), 2.04 (m, 2 H), 1.28 (t, 3 H)

**STEP 1 : Preparation of ethyl 3-[1-(3-{[2-(benzyloxy)ethyl](methyl)amino}propyl)-4-methyl-1H-benzotriazol-5-yl]-3-{3-[(1S)-1-hydroxyethyl]-4-methylphenyl}propanoate**

20

Using General Procedure 6 starting from ethyl (2E)-3-[1-(3-{[2-(benzyloxy)ethyl](methyl)amino}propyl)-4-methyl-1H-benzotriazol-5-yl]prop-2-enoate (1 eq.) and (1S)-1-[2-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]ethanol (1 eq.) as reactants, the title compound (30% yield) was obtained.

**<sup>1</sup>H-NMR** (400 MHz, DMSO-d<sub>6</sub>) δ ppm: 7.57/7.44 (d, 2 H), 7.4 (d, 1 H), 7.35-7.22 (d, 5 H), 7.03 (d, 1 H), 6.99 (dd, 1 H), 4.98 (d, 1 H), 4.82 (m, 1 H), 4.82 (m, 1 H), 4.63 (m, 2 H), 4.4 (s, 2 H), 3.92 (q, 2 H), 3.49 (t, 2 H), 3.11 (m, 2 H), 2.77 (s, 3 H), 2.5 (m, 2 H), 2.32 (m, 2 H), 2.17 (s, 3 H), 2.17 (s, 3 H), 2.01 (quint, 2 H), 1.22 (d, 3 H), 1 (t, 3 H)

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**STEP 2 : Preparation of ethyl 3-(3-((1*R*)-1-[6-(benzyloxy)-2,2-dioxo-2*H*-1,2λ<sup>6</sup>,3-benzoxathiazin-3(4*H*)-yl]ethyl)-4-methylphenyl)-3-[1-(3-{[2-(benzyloxy)ethyl](methyl)amino}propyl)-4-methyl-1*H*-benzotriazol-5-yl]propanoate**

5 Using General Procedure 7 starting from ethyl 3-[1-(3-{[2-(benzyloxy)ethyl](methyl)amino}propyl)-4-methyl-1*H*-benzotriazol-5-yl]-3-{3-[(1*S*)-1-hydroxyethyl]-4-methylphenyl}propanoate (1 eq.) and 6-(benzyloxy)-3,4-dihydro-2*H*-1,2λ<sup>6</sup>,3-benzoxathiazine-2,2-dione (1.1 eq.) as reactants, the title compound (92% yield) was obtained. <sup>1</sup>H-NMR (400 MHz, DMSO-d<sub>6</sub>) δ ppm: 0.97 (td, J=7.06, 4.95 Hz, 2 H) 1.41 (d, J=6.97 Hz, 2 H) 2.12 (d, J=2.93 Hz, 4 H) 2.21 - 2.32 (m, 4 H) 2.76 (d, J=3.79 Hz, 2 H) 3.11 - 3.25 (m, 2 H) 3.44 (d, J=4.28 Hz, 1 H) 3.92 (d, J=7.09 Hz, 1 H) 4.38 (d, J=4.65 Hz, 3 H) 4.60 (s, 1 H) 4.79 - 4.95 (m, 1 H) 4.98 - 5.17 (m, 2 H) 5.20 - 5.35 (m, 1 H) 6.77 - 7.65 (m, 14 H)

**STEP 3 : Preparation of ethyl 3-{3-[(1*R*)-1-(6-hydroxy-2,2-dioxo-2*H*-1,2λ<sup>6</sup>,3-benzoxathiazin-3(4*H*)-yl)ethyl]-4-methylphenyl}-3-[1-(3-{[2-(benzyloxy)ethyl](methyl)amino}propyl)-4-methyl-1*H*-benzotriazol-5-yl]propanoate**

Using General Procedure 8 starting from ethyl 3-(3-((1*R*)-1-[6-(benzyloxy)-2,2-dioxo-2*H*-1,2λ<sup>6</sup>,3-benzoxathiazin-3(4*H*)-yl]ethyl)-4-methylphenyl)-3-[1-(3-{[2-(benzyloxy)ethyl](methyl)amino}propyl)-4-methyl-1*H*-benzotriazol-5-yl]propanoate (1 eq.) as a reactant, the title compound (white solid, 95% yield) was obtained.

<sup>1</sup>H-NMR (400 MHz, DMSO-d<sub>6</sub>) δ ppm: 9.64 (s, 1 H), 7.62/7.56 (2d+2d, 2 H), 7.46 (2s, 1 H), 7.11 (m, 2 H), 6.91 (2d, 1 H), 6.72 (m, 1 H), 6.57 (2d, 1 H), 5.25 (q, 1 H), 4.87 (q, 1 H), 4.66 (t, 2 H), 4.36-4.25 (m, 3 H), 3.94 (2q, 2 H), 3.43 (t, 2 H), 3.22 (d, 2 H), 2.76 (s, 3 H), 2.35 (2t, 2 H), 2.31-2.27 (m, 2 H), 2.27 (s, 3 H), 2.12 (2s, 3 H), 2 (q, 2 H), 1.42 (2d, 3 H), 1 (2t, 3 H)

**STEP 4 : Preparation of ethyl 3-(1-{3-[(2-chloroethyl)(methyl)amino]propyl}-4-methyl-1*H*-benzotriazol-5-yl)-3-{3-[(1*R*)-1-(6-hydroxy-2,2-dioxo-2*H*-1,2λ<sup>6</sup>,3-benzoxathiazin-3(4*H*)-yl)ethyl]-4-methylphenyl}propanoate hydrochloride**

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Using General Procedure 10 starting from ethyl 3-{3-[(1*R*)-1-(6-hydroxy-2,2-dioxo-2*H*-1,2λ<sup>6</sup>,3-benzoxathiazin-3(4*H*)-yl)ethyl]-4-methylphenyl}-3-(1-{3-[(2-hydroxyethyl)(methyl)amino]propyl}-4-methyl-1*H*-benzotriazol-5-yl)propanoate (1 eq.) as a reactant, the title compound (white solid, 90% yield) was obtained.

5 <sup>1</sup>H-NMR (400 MHz, DMSO-d<sub>6</sub>) δ ppm: 10.32 (2s, 1 H), 9.7 (sl, 1 H), 7.74-7.62 (d, 2 H), 7.5 (s, 1 H), 7.13-7.08 (m, 2 H), 6.92 (d, 1 H), 6.74 (t, 1 H), 6.66/6.57 (d, 1 H), 5.26 (quint, 1 H), 4.89 (q, 1 H), 4.75 (q, 2 H), 4.35 (d, 2 H), 3.96 (q, 4 H), 3.94 (t, 2 H), 3.54-3.38 (m, 2 H), 3.3-3.11 (m, 4 H), 2.77 (m, 6 H), 2.36-2.26 (m, 2 H), 2.3 (s, 3 H), 1.43 (t, 3 H), 1.04 (2t, 3 H)

10 **STEP 5 : Preparation of ethyl [(2*R*)-2,4,20,33-tetramethyl-29,29-dioxo-23,28-dioxa-29λ<sup>6</sup>-thia-1,14,15,16,20-pentaazahexacyclo[22.5.3.1<sup>3,7</sup>.1<sup>9,13</sup>.0<sup>12,16</sup>.0<sup>27,31</sup>]tetratriaconta-3(34),4,6,9(33),10,12,14,24,26,31-decaen-8-yl]acetate**

Using General Procedure 11 starting from ethyl 3-(1-{3-[(2-chloroethyl)(methyl)amino]propyl}-4-methyl-1*H*-benzotriazol-5-yl)-3-{3-[(1*R*)-1-(6-hydroxy-2,2-dioxo-2*H*-1,2λ<sup>6</sup>,3-benzoxathiazin-3(4*H*)-yl)ethyl]-4-methylphenyl}propanoate hydrochloride (1 eq.) as a reactant, the title compound (white solid, 96% yield) was obtained.

15 <sup>1</sup>H-NMR (400 MHz, DMSO-d<sub>6</sub>) δ ppm: 7.85/7.71 (dd, 1 H), 7.63/7.06 (dd, 1 H), 7.56/6.85 (d, 1 H), 7.45/7.31 (dd, 1 H), 7.28/7.11 (d, 1 H), 7.05/6.98 (d, 1 H), 6.91/6.82 (dd, 1 H), 6.28/6.06 (d, 1 H), 5.34-5.21 (m, 1 H), 4.95/4.88 (t, 1 H), 4.83-4.53 (m, 2 H), 4.12/4.03/3.78/3.66 (2dd, 2 H), 4.03-3.73 (m, 2 H), 3.91 (q, 2 H), 3.4-2.91 (2ddd, 2 H), 2.83/2.81 (2s, 3 H), 2.72-2.38 (m, 4 H), 2.35-2.03 (m, 2 H), 2.32/2.3/2.27 (3s, 6 H), 1.5/1.15 (2d, 3 H), 1.03/1 (2t, 3 H)

#### 25 **STEP 6 : Preparation of EXAMPLE 34**

Using General Procedure 12 starting from ethyl [(2*R*)-2,4,20,33-tetramethyl-29,29-dioxo-23,28-dioxa-29λ<sup>6</sup>-thia-1,14,15,16,20-pentaazahexacyclo[22.5.3.1<sup>3,7</sup>.1<sup>9,13</sup>.0<sup>12,16</sup>.0<sup>27,31</sup>]tetratriaconta-3(34),4,6,9(33),10,12,14,24,26,31-decaen-8-yl]acetate (1 eq.) as a reactant, the title compound (white solid, 68% yield) was obtained.

30 The diastereo-pure products were obtained by chromatographic separation on chiral column.



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**Example 34a (2R,8S)**

**HRMS** calculated for  $C_{32}H_{37}N_5O_6S$ : 619.2464;  $[M+H]^+$  found: 620.2536 ( $\delta = -0.2$  ppm)

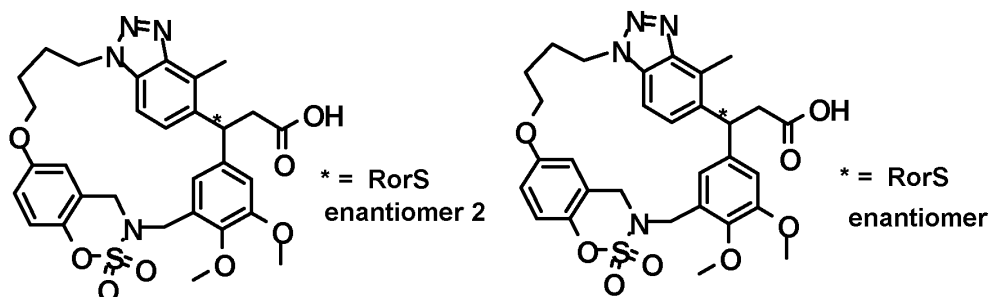
**$^1H$ -NMR** (400 MHz, DMSO- $d_6$ )  $\delta$  ppm: 12.1 (m, 1 H), 7.83/7.71 (d, 2 H), 7.54 (d, 1 H), 7.31 (dd, 1 H), 7.11 (d, 1 H), 7.04 (d, 1 H), 6.91 (dd, 1 H), 6.28 (d, 1 H), 5.31 (q, 1 H), 4.85 (t, 1 H), 4.82-4.68 (m, 2 H), 4.11/3.65 (dd, 2 H), 3.99 (t, 2 H), 3.22/3.05 (2dd, 2 H), 2.85-2.44 (m, 4 H), 2.82 (s, 3 H), 2.3/2.28 (2s, 6 H), 2.12 (m, 2 H), 1.49 (d, 3 H)

**Example 34b (2R,8R)**

**HRMS** calculated for  $C_{32}H_{37}N_5O_6S$ : 619.2464;  $[M+H]^+$  found: 620.2536 ( $\delta = -0.2$  ppm)

**$^1H$ -NMR** (400 MHz, DMSO- $d_6$ )  $\delta$  ppm: 12.3 (m, 1 H), 7.62/7.3 (dd, 1 H), 7.46 (dd, 1 H), 7.03 (d, 1 H), 6.98 (d, 1 H), 6.84 (d, 1 H), 6.83 (dd, 1 H), 6.07 (d, 1 H), 5.27 (q, 1 H), 4.93 (t, 1 H), 4.74/4.58 (2m, 2 H), 4.03/3.77 (dd, 2 H), 3.88-3.75 (m, 2 H), 3.15/2.83 (2dd, 2 H), 2.81 (s, 3 H), 2.68 (m, 2 H), 2.54 (m, 2 H), 2.33/2.3 (2s, 3 H), 2.2 (m, 2 H), 1.15 (d, 3 H)

**EXAMPLE 35** : [4,5-Dimethoxy-31-methyl-27,27-dioxo-21,26-dioxa-27 $\lambda^6$ -thia-1,14,15,16-tetraazahexacyclo[20.5.3.1<sup>3,7</sup>.1<sup>9,13</sup>.0<sup>12,16</sup>.0<sup>25,29</sup>]dotriaconta-3(32),4,6,9(31),10,12,14,22,24,29-decaen-8-yl]acetic acid



**STEP B1** : Preparation of [2,3-dimethoxy-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]methanol

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Using General Procedure 3 starting from (5-bromo-2,3-dimethoxyphenyl)methanol (1 eq., 18.0 g., 72.9 mmol) as a reactant, gave the title compound (11.10 g, 52% yield)

<sup>1</sup>H-NMR (400 MHz, DMSO-d<sub>6</sub>) δ ppm: 7.4 (sl, 1 H), 7.13 (sl, 1 H), 5.04 (t, 1 H), 4.5 (d, 2 H), 3.81/3.73 (2s, 6 H), 1.29 (s, 12 H)

5

**STEP 1 : Preparation of ethyl 3-{1-[4-(benzyloxy)butyl]-4-methyl-1H-benzotriazol-5-yl}-3-[3-(hydroxymethyl)-4,5-dimethoxyphenyl]propanoate**

Using General Procedure 6 starting from ethyl (2E)-3-{1-[4-(benzyloxy)butyl]-4-methyl-1H-benzotriazol-5-yl}prop-2-enoate (1 eq.) and [2,3-dimethoxy-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]methanol (1 eq.) as reactants, the title compound (61% yield) was obtained.

<sup>1</sup>H-NMR (400 MHz, DMSO-d<sub>6</sub>) δ ppm: 7.6/7.52 (2d, 2 H), 7.33-7.23 (m, 5 H), 6.95 (d, 1 H), 6.88 (d, 1 H), 4.93 (t, 1 H), 4.83 (t, 1 H), 4.66 (t, 2 H), 4.42 (d, 2 H), 4.4 (m, 2 H), 3.93 (q, 2 H), 3.77/3.63 (2s, 6 H), 3.42 (t, 2 H), 3.16 (d, 2 H), 2.78 (s, 3 H), 1.94 (quint, 2 H), 1.5 (quint, 2 H), 0.99 (t, 3 H)

15

**STEP 2 : Preparation of ethyl 3-{1-[4-(benzyloxy)butyl]-4-methyl-1H-benzotriazol-5-yl}-3-{3-[[6-(benzyloxy)-2,2-dioxo-2H-1,2λ<sup>6</sup>,3-benzoxathiazin-3(4H)-yl]methyl]-4,5-dimethoxyphenyl}propanoate**

20

Using General Procedure 7 starting from ethyl 3-{1-[4-(benzyloxy)butyl]-4-methyl-1H-benzotriazol-5-yl}-3-[3-(hydroxymethyl)-4,5-dimethoxyphenyl]propanoate (1 eq.) and 6-(benzyloxy)-3,4-dihydro-2H-1,2λ<sup>6</sup>,3-benzoxathiazine-2,2-dione (1.1 eq.) as reactants, the title compound (97% yield) was obtained.

25

<sup>1</sup>H-NMR (400 MHz, DMSO-d<sub>6</sub>) δ ppm: 7.6 (d, 1 H), 7.52 (d, 1 H), 7.48-7.2 (m, 10 H), 7.02 (m, 3 H), 6.92 (d, 1 H), 6.88 (d, 1 H), 5.09 (s, 2 H), 4.82 (t, 1 H), 4.62 (t, 2 H), 4.5 (s, 2 H), 4.39 (s, 2 H), 4.2 (s, 2 H), 3.92 (q, 2 H), 3.78 (s, 3 H), 3.61 (s, 3 H), 3.4 (t, 2 H), 3.19 (m, 2 H), 2.79 (s, 3 H), 1.91 (m, 2 H), 1.49 (m, 2 H), 0.99 (t, 3 H)

30

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**STEP 3 : Preparation of ethyl 3-[1-(4-hydroxybutyl)-4-methyl-1*H*-benzotriazol-5-yl]-3-{3-[(6-hydroxy-2,2-dioxo-2*H*-1,2λ<sup>6</sup>,3-benzoxathiazin-3(4*H*)-yl)methyl]-4,5-dimethoxyphenyl}propanoate**

5 Using General Procedure 8 starting from ethyl 3-{1-[4-(benzyloxy)butyl]-4-methyl-1*H*-benzotriazol-5-yl}-3-(3-{[6-(benzyloxy)-2,2-dioxo-2*H*-1,2λ<sup>6</sup>,3-benzoxathiazin-3(4*H*)-yl]methyl}-4,5-dimethoxyphenyl)propanoate (1 eq.) as a reactant, the title compound (87% yield) was obtained.

<sup>1</sup>H-NMR (400 MHz, DMSO-d<sub>6</sub>) δ ppm: 9.65/4.85 (s+t, 2 H), 7.62 (d, 1 H), 7.58 (d, 1 H), 7.02  
10 (d, 1 H), 6.91 (d, 1 H), 6.88 (d, 1 H), 6.8 (m, 1 H), 6.75 (dd, 1 H), 4.66 (t, 2 H), 4.45 (s, 2 H), 4.41 (m, 1 H), 4.2 (m, 2 H), 3.95 (q, 2 H), 3.78 (s, 3 H), 3.68 (s, 3 H), 3.4 (t, 2 H), 3.2 (dd, 2 H), 2.8 (s, 3 H), 1.91 (m, 2 H), 1.39 (m, 2 H), 1 (t, 3 H)

**STEP 4 : Preparation of ethyl 3-[1-(4-bromobutyl)-4-methyl-1*H*-benzotriazol-5-yl]-3-{3-[(6-hydroxy-2,2-dioxo-2*H*-1,2λ<sup>6</sup>,3-benzoxathiazin-3(4*H*)-yl)methyl]-4,5-dimethoxyphenyl}propanoate**

Using General Procedure 9 starting from ethyl 3-[1-(4-hydroxybutyl)-4-methyl-1*H*-benzotriazol-5-yl]-3-{3-[(6-hydroxy-2,2-dioxo-2*H*-1,2λ<sup>6</sup>,3-benzoxathiazin-3(4*H*)-yl)methyl]-4,5-dimethoxyphenyl}propanoate (1 eq.) as a reactant, the title compound (white solid, 91%  
20 yield) was obtained.

<sup>1</sup>H-NMR (400 MHz, DMSO-d<sub>6</sub>) δ ppm: 9.63 (s, 1 H), 7.65 (d, 1 H), 7.58 (d, 1 H), 7.02 (d, 1 H), 6.91 (d, 1 H), 6.86 (d, 1 H), 6.74 (dd, 1 H), 6.6 (d, 1 H), 4.84 (t, 1 H), 4.69 (t, 2 H), 4.45 (sl, 2 H), 4.2/4.15 (2d, 2 H), 3.94 (q, 2 H), 3.76 (s, 3 H), 3.63 (s, 3 H), 3.54 (t, 2 H), 3.19 (dd, 2 H),  
25 2.79 (s, 3 H), 2 (m, 2 H), 1.77 (m, 2 H), 1 (t, 3 H)

**STEP 5 : Preparation of ethyl [4,5-dimethoxy-31-methyl-27,27-dioxo-21,26-dioxa-27λ<sup>6</sup>-thia-1,14,15,16-tetraazahexacyclo[20.5.3.1<sup>3,7</sup>.1<sup>9,13</sup>.0<sup>12,16</sup>.0<sup>25,29</sup>]dotriacont-3(32),4,6,9(31),10,12,14,22,24,29-decaen-8-yl]acetate**

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Using General Procedure 11 starting from ethyl 3-[1-(4-bromobutyl)-4-methyl-1*H*-benzotriazol-5-yl]-3-{3-[(6-hydroxy-2,2-dioxo-2*H*-1,2λ<sup>6</sup>,3-benzoxathiazin-3(4*H*)-yl)methyl]-4,5-dimethoxyphenyl} propanoate (1 eq.) as a reactant, the title compound (white solid, 70% yield) was obtained.

- 5    <sup>1</sup>H-NMR (400 MHz, DMSO-d<sub>6</sub>) δ ppm: 7.68 (d, 1 H), 7.47 (d, 1 H), 7.34 (d, 1 H), 6.97 (d, 1 H), 6.79 (dd, 1 H), 6.11 (d, 1 H), 5.85 (d, 1 H), 4.83-4.72 (m, 3 H), 4.09-3.63 (m, 6 H), 3.92 (s, 3 H), 3.76 (s, 3 H), 3.69/3.47 (2m, 2 H), 3.25/3.09 (2dd, 2 H), 2.65 (s, 3 H), 2.21/2.07 (2m, 2 H), 1.81/1.63 (2m, 2 H), 1 (t, 3 H)

10    **STEP 6 : Preparation of EXAMPLE 35**

Using General Procedure 12 starting from ethyl [4,5-dimethoxy-31-methyl-27,27-dioxo-21,26-dioxa-27λ<sup>6</sup>-thia-1,14,15,16-tetraazahexacyclo[20.5.3.1<sup>3,7</sup>.1<sup>9,13</sup>.0<sup>12,16</sup>.0<sup>25,29</sup>]dotriaconta-3(32),4,6,9(31),10,12,14,22,24,29-decaen-8-yl]acetate (1 eq.) as a reactant, the title

15    compound (97% yield) was obtained.

The enantiopure products were obtained by chromatographic separation on chiral column.

**Example 35a (E2)**

HRMS calculated for C<sub>30</sub>H<sub>32</sub>N<sub>4</sub>O<sub>8</sub>S: 608.1941; [M+H]<sup>+</sup> found: 609.2013 (δ=-0.1 ppm)

20

**Example 35b (E1)**

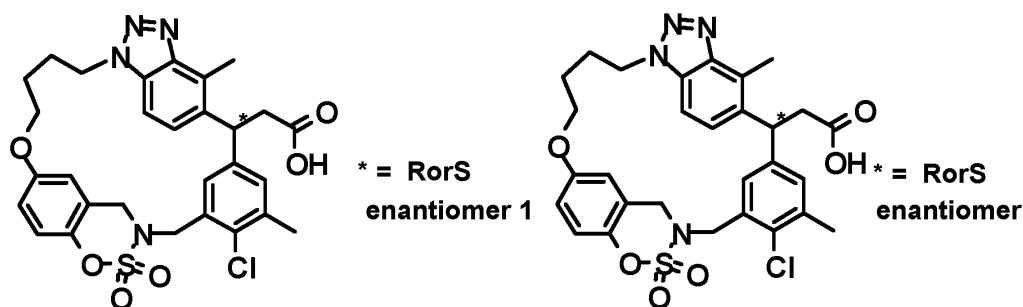
HRMS calculated for C<sub>30</sub>H<sub>32</sub>N<sub>4</sub>O<sub>8</sub>S: 608.1941; [M+H]<sup>+</sup> found: 609.2013 (δ=-0.1 ppm)

- <sup>1</sup>H-NMR (400 MHz, DMSO-d<sub>6</sub>) δ ppm: 12.15 (m, 1 H), 7.7 (d, 1 H), 7.49 (d, 1 H), 7.38 (d, 1 H), 6.99 (d, 1 H), 6.8 (dd, 1 H), 6.1 (d, 1 H), 5.82 (d, 1 H), 4.8 (m, 3 H), 4.1 (2d, 2 H), 3.92/3.75
- 25    (2s, 6 H), 3.91/3.85 (2d, 2 H), 3.7/3.45 (2m, 2 H), 3.15/3 (2dd, 2 H), 2.65 (s, 3 H), 2.2/2.1 (2m, 2 H), 1.82/1.65 (2m, 2 H)

**EXAMPLE 36 : [4-Chloro-5,31-dimethyl-27,27-dioxo-21,26-dioxa-27λ<sup>6</sup>-thia-1,14,15,16-tetraazahexacyclo[20.5.3.1<sup>3,7</sup>.1<sup>9,13</sup>.0<sup>12,16</sup>.0<sup>25,29</sup>]dotriaconta-3(32),4,6,9(31),10,12,14,22,24,29-decaen-8-yl]acetic acid**

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#### STEP B1 : Preparation of (5-bromo-2-chloro-3-methylphenyl)methanol

5

Methyl 5-bromo-2-chloro-3-methylbenzoate (1 eq., 24.0 g, 91 mmol) was dissolved in EtOH (300mL), then sodium borohydride (3 eq., 10.4 g, 273 mmol) was added to the stirred mixture at 0 °C. The mixture was stirred at this temperature for 10 min before addition of calcium chloride (3 eq., 30.3 g, 273 mmol) over 30min, then was allowed to warm to RT and stirred for 2h. The reaction mixture was quenched with cold 1M aq. HCl solution, extracted with EtOAc, the organic phase was separated, dried over MgSO<sub>4</sub>, concentrated under reduced pressure to give the crude product (19.0 g, 88% yield) as white solid, which was used in the next step without further purification.

<sup>1</sup>H-NMR (400 MHz, DMSO-d<sub>6</sub>) δ ppm: 7.51 (s, 2 H), 5.54 (t, 1 H), 4.53 (d, 2 H), 2.32 (s, 3 H)

15

#### STEP B2 : Preparation of [2-chloro-3-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]methanol

Using General Procedure 3 starting from (5-bromo-2-chloro-3-methylphenyl)methanol (1 eq., 19.0 g., 80.7 mmol) as a reactant, the title compound (15.15 g, 66% yield) was obtained.

<sup>1</sup>H-NMR (400 MHz, DMSO-d<sub>6</sub>) δ ppm: 7.78 (d, 1 H), 7.51 (d, 1 H), 5.4 (t, 1 H), 4.55 (d, 2 H), 2.32 (s, 3 H), 1.3 (s, 12 H)

20

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**STEP 1 : Preparation of ethyl 3-[4-chloro-3-(hydroxymethyl)-5-methylphenyl]-3-(1-{4-[(4-methoxyphenyl)methoxy]butyl}-4-methyl-1*H*-benzotriazol-5-yl)propanoate**

5 Using General Procedure 6 starting from ethyl (2*E*)-3-(1-{4-[(4-methoxyphenyl)methoxy]butyl}-4-methyl-1*H*-benzotriazol-5-yl)prop-2-enoate (1 eq.) and [2-chloro-3-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]methanol (1.5 eq.) as reactants, the title compound (yellow oil, 50% yield) was obtained.

<sup>1</sup>H-NMR (400 MHz, DMSO-d<sub>6</sub>) δ ppm: 7.6 (d, 1 H), 7.45 (d, 1 H), 7.3/7.25 (2d, 2 H), 7.2 (d,  
10 2 H), 6.9 (d, 2 H), 5.3 (t, 1 H), 4.85 (t, 1 H), 4.65 (t, 2 H), 4.5 (d, 2 H), 4.3 (s, 2 H), 3.95 (q, 2 H), 3.75 (s, 3 H), 3.4 (t, 2 H), 3.2 (2dd, 2 H), 2.8 (s, 3 H), 2.3 (s, 3 H), 1.9 (quint, 2 H), 1.5 (quint, 2 H), 1 (t, 3 H)

**STEP 2 : Preparation of ethyl 3-(3-{[6-(benzyloxy)-2,2-dioxo-2*H*-1,2λ<sup>6</sup>,3-benzoxathiazin-3(4*H*)-yl]methyl}-4-chloro-5-methylphenyl)-3-(1-{4-[(4-methoxyphenyl)methoxy]butyl}-4-methyl-1*H*-benzotriazol-5-yl)propanoate**

Using General Procedure 7 starting from ethyl 3-[4-chloro-3-(hydroxymethyl)-5-methylphenyl]-3-(1-{4-[(4-methoxyphenyl)methoxy]butyl}-4-methyl-1*H*-benzotriazol-5-yl)propanoate (1 eq.) and 6-(benzyloxy)-3,4-dihydro-2*H*-1,2λ<sup>6</sup>,3-benzoxathiazine-2,2-dione (1.1 eq.) as reactants, the title compound (91% yield) was obtained.

<sup>1</sup>H-NMR (400 MHz, DMSO-d<sub>6</sub>) δ ppm: 7.6/7.5 (2d, 2 H), 7.45 (dl, 2 H), 7.4 (t, 2 H), 7.35 (m, 3 H), 7.2 (d, 2 H), 7.1 (d+dd, 2 H), 6.95 (d, 1 H), 6.85 (d, 2 H), 5.1 (s, 2 H), 4.9 (t, 1 H), 4.6 (t, 2 H), 4.55 (sl, 2 H), 4.35 (sl, 2 H), 4.3 (s, 2 H), 3.9 (q, 2 H), 3.7 (s, 3 H), 3.4 (t, 2 H), 3.2 (2dd,  
25 2 H), 2.8 (s, 3 H), 2.3 (s, 3 H), 1.9 (quint, 2 H), 1.15 (quint, 2 H), 1 (t, 3 H)

**STEP 3 : Preparation of ethyl 3-[4-chloro-3-[(6-hydroxy-2,2-dioxo-4*H*-1,2λ<sup>6</sup>,3-benzoxathiazin-3-yl)methyl]-5-methyl-phenyl]-3-[1-(4-hydroxybutyl)-4-methyl-benzotriazol-5-yl]propanoate**

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Using General Procedure 8 starting from ethyl 3-(3-{{6-(benzyloxy)-2,2-dioxo-2*H*-1,2λ<sup>6</sup>,3-benzoxathiazin-3(4*H*)-yl}methyl}-4-chloro-5-methylphenyl)-3-(1-{{4-((4-methoxyphenyl)methoxy)butyl}-4-methyl-1*H*-benzotriazol-5-yl}propanoate (1 eq.) as a reactant, the title compound (97% yield) was obtained.

- 5 <sup>1</sup>H-NMR (400 MHz, DMSO-d<sub>6</sub>) δ ppm: 9.6 (m, 1 H), 7.6 (d, 1 H), 7.5 (d, 1 H), 7.3 (2d, 2 H), 6.95 (d, 1 H), 6.8 (dd, 1 H), 6.6 (d, 1 H), 4.95 (t, 1 H), 4.65 (t, 2 H), 4.5 (sl, 2 H), 4.4 (m, 1 H), 4.3 (sl, 2 H), 3.95 (q, 2 H), 3.4 (m, 2 H), 3.2 (m, 2 H), 2.8 (s, 3 H), 2.3 (s, 3 H), 1.9 (quint, 2 H), 1.4 (quint, 2 H), 1 (t, 3 H)

- 10 **STEP 4 : Preparation of ethyl 3-[1-(4-bromobutyl)-4-methyl-1*H*-benzotriazol-5-yl]-3-{4-chloro-3-[(6-hydroxy-2,2-dioxo-2*H*-1,2λ<sup>6</sup>,3-benzoxathiazin-3(4*H*)-yl)methyl]-5-methylphenyl}propanoate**

- Using General Procedure 9 starting from ethyl 3-[4-chloro-3-[(6-hydroxy-2,2-dioxo-4*H*-1,2λ<sup>6</sup>,3-benzoxathiazin-3-yl)methyl]-5-methyl-phenyl]-3-[1-(4-hydroxybutyl)-4-methyl-benzotriazol-5-yl]propanoate (1 eq.) as a reactant, the title compound (70% yield) was obtained.
- 15 <sup>1</sup>H-NMR (400 MHz, DMSO-d<sub>6</sub>) δ ppm: 9.66 (s, 1 H), 7.65 (d, 1 H), 7.53 (d, 1 H), 7.33 (2d, 2 H), 6.96 (d, 1 H), 6.77 (dd, 1 H), 6.61 (d, 1 H), 4.85 (t, 1 H), 4.69 (t, 2 H), 4.5 (s, 2 H), 4.32 (m, 2 H), 3.95 (q, 2 H), 3.54 (t, 2 H), 3.19 (dd, 2 H), 2.78 (s, 3 H), 2.28 (s, 3 H), 2 (m, 2 H), 1.77 (m, 2 H), 1.01 (t, 3 H)
- 20

**STEP 5 : Preparation of ethyl [4-chloro-5,31-dimethyl-27,27-dioxo-21,26-dioxa-27λ<sup>6</sup>-thia-1,14,15,16-tetraazahexacyclo[20.5.3.1<sup>3,7</sup>.1<sup>9,13</sup>.0<sup>12,16</sup>.0<sup>25,29</sup>]dotriacont-3(32),4,6,9(31),10,12,14,22,24,29-decaen-8-yl]acetate**

25

Using General Procedure 11 starting from ethyl 3-[1-(4-bromobutyl)-4-methyl-1*H*-benzotriazol-5-yl]-3-{4-chloro-3-[(6-hydroxy-2,2-dioxo-2*H*-1,2λ<sup>6</sup>,3-benzoxathiazin-3(4*H*)-yl)methyl]-5-methylphenyl}propanoate (1 eq.) as a reactant, the title compound (colorless solid, 85% yield) was obtained.

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<sup>1</sup>H-NMR (400 MHz, DMSO-d<sub>6</sub>) δ ppm: 7.7 (d, 1 H), 7.62 (s, 1 H), 7.45 (d, 1 H), 7 (s, 1 H), 6.8 (dd, 1 H), 6.7 (s, 1 H), 6.6 (s, 1 H), 4.8 (t, 2 H), 4.8 (t, 1 H), 4.25/3.8 (d, 2 H), 4.05 (d, 2 H), 3.92 (q, 2 H), 3.7/3.45 (m, 2 H), 3.2/3.1 (dd, 2 H), 2.65 (s, 3 H), 2.4 (s, 3 H), 2.2-2 (m, 2 H), 1.8/1.65 (m, 2 H), 1 (t, 3 H)

5

#### STEP 6 : Preparation of EXAMPLE 36

Using General Procedure 12 starting from ethyl [4-chloro-5,31-dimethyl-27,27-dioxo-21,26-dioxa-27λ<sup>6</sup>-thia-1,14,15,16-tetraazahexacyclo[20.5.3.1<sup>3,7</sup>.1<sup>9,13</sup>.0<sup>12,16</sup>.0<sup>25,29</sup>]dotriaconta-

10 3(32),4,6,9(31),10,12,14,22,24,29-decaen-8-yl]acetate (1 eq.) as a reactant, the title compound (78% yield) was obtained.

The enantiopure products were obtained by chromatographic separation on chiral column.

#### Example 36a (E1)

15 HRMS calculated for C<sub>29</sub>H<sub>29</sub>ClN<sub>4</sub>O<sub>6</sub>S: 596.1496; [M+H]<sup>+</sup> found: 597.1574 (δ=0.8 ppm)

#### Example 36b (E2)

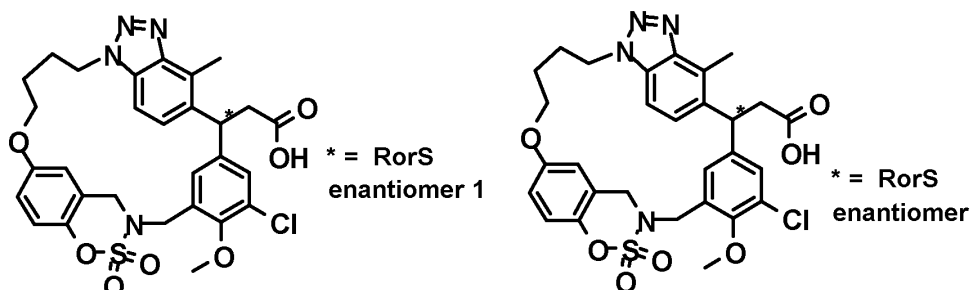
HRMS calculated for C<sub>29</sub>H<sub>29</sub>ClN<sub>4</sub>O<sub>6</sub>S: 596.1496; [M+H]<sup>+</sup> found: 597.1573 (δ=0.7 ppm)

<sup>1</sup>H-NMR (400 MHz, DMSO-d<sub>6</sub>) δ ppm: 12.3 (m, 1 H), 7.7 (d+d, 2 H), 7.45 (d, 1 H), 7 (d, 1 H), 6.8 (dd, 1 H), 6.6 (d, 1 H), 5.8 (d, 1 H), 4.8 (m, 3 H), 4.25/4 (d, 2 H), 4/3.8 (d, 2 H), 3.65/3.4 (m, 2 H), 3.1/2.95 (dd, 2 H), 2.65 (sl, 3 H), 2.4 (s, 3 H), 2.2/2.1 (m, 2 H), 1.8/1.65 (m, 2 H)

25 **EXAMPLE 37 : [5-Chloro-4-methoxy-31-methyl-27,27-dioxo-21,26-dioxa-27λ<sup>6</sup>-thia-1,14,15,16-tetraazahexacyclo[20.5.3.1<sup>3,7</sup>.1<sup>9,13</sup>.0<sup>12,16</sup>.0<sup>25,29</sup>]dotriaconta-3(32),4,6,9(31),10,12,14,22,24,29-decaen-8-yl]acetic acid**



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**STEP B1 : Preparation of [3-chloro-2-methoxy-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]methanol**

5

Using General Procedure 3 starting from (5-bromo-3-chloro-2-methoxy-phenyl)methanol (1 eq., 17.0 g., 67.6 mmol) as a reactant, the title compound (11 g, 55% yield) was obtained.

<sup>1</sup>H-NMR (400 MHz, DMSO-d<sub>6</sub>) δ ppm: 7.73 (d, 1 H), 7.54 (d, 1 H), 5.26 (t, 1 H), 4.56 (d, 2 H), 3.78 (s, 3 H), 1.29 (s, 12 H)

10

**STEP 1 : Preparation of ethyl 3-{1-[4-(benzyloxy)butyl]-4-methyl-1H-benzotriazol-5-yl}-3-[3-chloro-5-(hydroxymethyl)-4-methoxyphenyl]propanoate**

Using General Procedure 6 starting from ethyl (2E)-3-{1-[4-(benzyloxy)butyl]-4-methyl-1H-benzotriazol-5-yl}prop-2-enoate (1 eq.) and [3-chloro-2-methoxy-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]methanol (1.05 eq.) as reactants, the title compound (60% yield) was obtained.

<sup>1</sup>H-NMR (400 MHz, DMSO-d<sub>6</sub>) δ ppm: 7.61 (d, 1 H), 7.5 (d, 1 H), 7.38-7.2 (m, 7 H), 5.18 (t, 1 H), 4.82 (t, 1 H), 4.68 (t, 2 H), 4.49 (d, 2 H), 4.4 (s, 2 H), 3.92 (q, 2 H), 3.7 (s, 3 H), 3.41 (t, 2 H), 3.18 (m, 2 H), 2.77 (s, 3 H), 1.95 (m, 2 H), 1.5 (m, 2 H), 1 (t, 3 H)

20

**STEP 2 : Preparation of ethyl 3-{1-[4-(benzyloxy)butyl]-4-methyl-1H-benzotriazol-5-yl}-3-{3-[[6-(benzyloxy)-2,2-dioxo-2H-1,2λ<sup>6</sup>,3-benzoxathiazin-3(4H)-yl]methyl]-5-chloro-4-methoxyphenyl}propanoate**

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Using General Procedure 7 starting from ethyl 3-{1-[4-(benzyloxy)butyl]-4-methyl-1*H*-benzotriazol-5-yl}-3-[3-chloro-5-(hydroxymethyl)-4-methoxyphenyl]propanoate (1 eq.) and 6-(benzyloxy)-3,4-dihydro-2*H*-1,2λ<sup>6</sup>,3-benzoxathiazine-2,2-dione (1.1 eq.) as reactants, the title compound (97% yield) was obtained.

<sup>1</sup>H-NMR (400 MHz, DMSO-d<sub>6</sub>) δ ppm: 7.62 (d, 1 H), 7.54 (d, 1 H), 7.45-7.25 (m, 12 H), 7.03 (m, 2 H), 6.96 (d, 1 H), 5.08 (s, 2 H), 4.85 (t, 1 H), 4.65 (t, 2 H), 4.57 (s, 2 H), 4.39 (s, 2 H), 4.29 (s, 2 H), 3.94 (q, 2 H), 3.7 (s, 3 H), 3.41 (t, 2 H), 3.2 (dd, 2 H), 2.77 (s, 3 H), 1.93 (quint, 2 H), 1.49 (quint, 2 H), 0.99 (t, 3 H)

**STEP 3 : Preparation of ethyl 3-{3-chloro-5-[(6-hydroxy-2,2-dioxo-2*H*-1,2λ<sup>6</sup>,3-benzoxathiazin-3(4*H*)-yl)methyl]-4-methoxyphenyl}-3-[1-(4-hydroxybutyl)-4-methyl-1*H*-benzotriazol-5-yl]propanoate**

Using General Procedure 8 starting from ethyl 3-{1-[4-(benzyloxy)butyl]-4-methyl-1*H*-benzotriazol-5-yl}-3-(3-{[6-(benzyloxy)-2,2-dioxo-2*H*-1,2λ<sup>6</sup>,3-benzoxathiazin-3(4*H*)-yl]methyl}-5-chloro-4-methoxyphenyl)propanoate (1 eq.) as a reactant, the title compound (80% yield) was obtained.

<sup>1</sup>H-NMR (400 MHz, DMSO-d<sub>6</sub>) δ ppm: 9.69 (sl, 1 H), 7.65 (d, 1 H), 7.56 (d, 1 H), 7.43/7.35 (2d, 2 H), 6.92 (d, 1 H), 6.75 (dd, 1 H), 6.62 (d, 1 H), 4.85 (t, 1 H), 4.66 (t, 2 H), 4.52 (s, 2 H), 4.27 (s, 2 H), 3.95 (q, 2 H), 3.71 (s, 3 H), 3.39 (t, 2 H), 3.2 (d, 2 H), 2.77 (s, 3 H), 1.91 (quint, 2 H), 1.37 (quint, 2 H), 1.01 (t, 3 H)

**STEP 4 : Preparation of ethyl 3-[1-(4-bromobutyl)-4-methyl-1*H*-benzotriazol-5-yl]-3-{3-chloro-5-[(6-hydroxy-2,2-dioxo-2*H*-1,2λ<sup>6</sup>,3-benzoxathiazin-3(4*H*)-yl)methyl]-4-methoxyphenyl}propanoate**

Using General Procedure 9 starting from ethyl 3-{3-chloro-5-[(6-hydroxy-2,2-dioxo-2*H*-1,2λ<sup>6</sup>,3-benzoxathiazin-3(4*H*)-yl)methyl]-4-methoxyphenyl}-3-[1-(4-hydroxybutyl)-4-methyl-

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1*H*-benzotriazol-5-yl]propanoate (1 eq.) as a reactant, the title compound (89% yield) was obtained.

**<sup>1</sup>H-NMR** (400 MHz, DMSO-d<sub>6</sub>) δ ppm: 9.65 (s, 1 H), 7.67 (d, 1 H), 7.57 (d, 1 H), 7.43/7.35 (2d, 2 H), 6.92 (d, 1 H), 6.75 (dd, 1 H), 6.62 (d, 1 H), 4.85 (t, 1 H), 4.7 (t, 2 H), 4.52/4.27 (2s, 4 H), 3.94 (q, 2 H), 3.71 (s, 3 H), 3.54 (t, 2 H), 3.2 (d, 2 H), 2.77 (s, 3 H), 2 (m, 2 H), 1.78 (m, 2 H), 1 (t, 3 H)

**STEP 5 : Preparation of ethyl [5-chloro-4-methoxy-31-methyl-27,27-dioxo-21,26-dioxo-27λ<sup>6</sup>-thia-1,14,15,16-tetraazahexacyclo[20.5.3.1<sup>3,7</sup>.1<sup>9,13</sup>.0<sup>12,16</sup>.0<sup>25,29</sup>]dotriaconta-3(32),4,6,9(31),10,12,14,22,24,29-decaen-8-yl]acetate**

Using General Procedure 11 starting from ethyl 3-[1-(4-bromobutyl)-4-methyl-1*H*-benzotriazol-5-yl]-3-{3-chloro-5-[(6-hydroxy-2,2-dioxo-2*H*-1,2λ<sup>6</sup>,3-benzoxathiazin-3(4*H*)-yl)methyl]-4-methoxyphenyl}propanoate (1 eq.) as a reactant, the title compound (61% yield) was obtained.

**<sup>1</sup>H-NMR** (400 MHz, DMSO-d<sub>6</sub>) δ ppm: 7.75 (d, 1 H), 7.68 (d, 1 H), 7.44 (d, 1 H), 6.98 (d, 1 H), 6.79 (dd, 1 H), 6.63 (d, 1 H), 5.93 (d, 1 H), 4.79 (m, 3 H), 4.14/4.03 (2d, 2 H), 4-3.9 (m, 4 H), 3.83 (s, 3 H), 3.73/3.53 (m+dt, 2 H), 3.26/3.07 (2dd, 2 H), 2.66 (s, 3 H), 2.2/2.06 (2m, 2 H), 1.78/1.59 (2m, 2 H), 1 (t, 3 H)

**STEP 6 : Preparation of EXAMPLE 37**

Using General Procedure 12 starting from ethyl [5-chloro-4-methoxy-31-methyl-27,27-dioxo-21,26-dioxo-27λ<sup>6</sup>-thia-1,14,15,16-tetraazahexacyclo[20.5.3.1<sup>3,7</sup>.1<sup>9,13</sup>.0<sup>12,16</sup>.0<sup>25,29</sup>]dotriaconta-3(32),4,6,9(31),10,12,14,22,24,29-decaen-8-yl]acetate (1 eq.) as a reactant, the title compound (white solid, quant.) was obtained.

The enantiopure products were obtained by chromatographic separation on chiral column.

**Example 37a (E1)**

**HRMS** calculated for C<sub>29</sub>H<sub>29</sub>ClN<sub>4</sub>O<sub>7</sub>S: 612.1445; [M+H]<sup>+</sup> found: 613.1523 (δ=0.8 ppm)

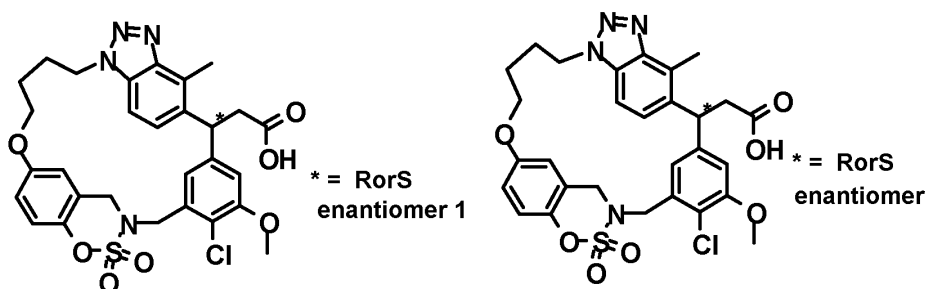
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**Example 37b (E2)**

**HRMS** calculated for  $C_{29}H_{29}ClN_4O_7S$ : 612.1445;  $[M+H]^+$  found: 613.1524 ( $\delta=0.9$  ppm)

**$^1H$ -NMR** (400 MHz, DMSO- $d_6$ )  $\delta$  ppm: 12.25 (m, 1 H), 7.75 (d, 1 H), 7.68 (d, 1 H), 7.43 (d, 1 H), 7 (d, 1 H), 6.8 (dd, 1 H), 6.62 (d, 1 H), 5.92 (d, 1 H), 4.79 (m, 3 H), 4.13/4.03 (2d, 2 H), 4.02-3.92 (dd, 2 H), 3.82 (s, 3 H), 3.72/3.52 (m+dt, 2 H), 3.12/2.98 (2dd, 2 H), 2.65 (s, 3 H), 2.21/2.08 (2m, 2 H), 1.79/1.6 (2m, 2 H)

**EXAMPLE 38** : [4-Chloro-5-methoxy-31-methyl-27,27-dioxo-21,26-dioxa-27 $\lambda^6$ -thia-1,14,15,16-tetraazahexacyclo[20.5.3.1<sup>3,7</sup>.1<sup>9,13</sup>.0<sup>12,16</sup>.0<sup>25,29</sup>]dotriacont-3(32),4,6,9(31),10,12,14,22,24,29-decaen-8-yl]acetic acid



**STEP B1 : Preparation of [2-chloro-3-methoxy-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]methanol**

Using General Procedure 3 starting from (5-bromo-2-chloro-3-methoxyphenyl)methanol (1 eq., 20.0 g., 79.5 mmol) as a reactant, gave the title compound (14.6 g, 62% yield).

**$^1H$ -NMR** (400 MHz, DMSO- $d_6$ )  $\delta$  ppm: 7.52 (d, 1 H), 7.19 (d, 1 H), 5.4 (t, 1 H), 4.55 (d, 2 H), 3.89 (s, 3 H), 1.3 (s, 12 H)

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**STEP 1 : Preparation of ethyl 3-[4-chloro-3-(hydroxymethyl)-5-methoxyphenyl]-3-(1-{4-[(4-methoxyphenyl)methoxy]butyl}-4-methyl-1*H*-benzotriazol-5-yl)propanoate**

5 Using General Procedure 6 starting from ethyl 3-(1-{4-[(4-methoxyphenyl)methoxy]butyl}-4-methyl-1*H*-benzotriazol-5-yl)propanoate (1 eq.) and [2-chloro-3-methoxy-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]methanol (1.5 eq.) as reactants, the title compound (yellow oil, 57% yield) was obtained.

<sup>1</sup>H-NMR (400 MHz, DMSO-d<sub>6</sub>) δ ppm: 7.6 (d, 1 H), 7.51 (d, 1 H), 7.2 (d, 2 H), 7.07/7.02 (2d, 10 2 H), 6.88 (d, 2 H), 5.28 (t, 1 H), 4.89 (t, 1 H), 4.63 (t, 2 H), 4.47 (d, 2 H), 4.3 (s, 2 H), 3.92 (q, 2 H), 3.81 (s, 3 H), 3.71 (s, 3 H), 3.39 (t, 2 H), 3.2 (d, 2 H), 2.79 (s, 3 H), 1.91 (m, 2 H), 1.49 (m, 2 H), 1 (t, 3 H)

**STEP 2 : Preparation of ethyl 3-(3-{[6-(benzyloxy)-2,2-dioxo-2*H*-1,2λ<sup>6</sup>,3-benzoxathiazin-3(4*H*)-yl]methyl}-4-chloro-5-methoxyphenyl)-3-(1-{4-[(4-methoxyphenyl)methoxy]butyl}-4-methyl-1*H*-benzotriazol-5-yl)propanoate**

Using General Procedure 7 starting from ethyl 3-[4-chloro-3-(hydroxymethyl)-5-methoxyphenyl]-3-(1-{4-[(4-methoxyphenyl)methoxy]butyl}-4-methyl-1*H*-benzotriazol-5-yl)propanoate (1 eq.) and 6-(benzyloxy)-3,4-dihydro-2*H*-1,2λ<sup>6</sup>,3-benzoxathiazine-2,2-dione (1.1 eq.) as reactants, the title compound (89% yield) was obtained.

<sup>1</sup>H-NMR (400 MHz, DMSO-d<sub>6</sub>) δ ppm: 7.59 (d, 1 H), 7.55 (d, 1 H), 7.46-7.32 (m, 5 H), 7.18 (d, 2 H), 7.14 (d, 1 H), 7.1-7.02 (m, 3 H), 6.93 (d, 1 H), 6.85 (d, 2 H), 5.08 (s, 2 H), 4.9 (t, 1 H), 4.62 (t, 2 H), 4.53 (s, 2 H), 4.31 (s, 2 H), 4.3 (s, 2 H), 3.94 (q, 2 H), 3.83 (s, 3 H), 3.72 (s, 3 25 H), 3.36 (t, 2 H), 3.23 (d, 2 H), 2.8 (s, 3 H), 1.9 (quint, 2 H), 1.46 (m, 2 H), 1 (t, 3 H)

**STEP 3 : Preparation of ethyl 3-{4-chloro-3-[(6-hydroxy-2,2-dioxo-2*H*-1,2λ<sup>6</sup>,3-benzoxathiazin-3(4*H*)-yl)methyl]-5-methoxyphenyl}-3-[1-(4-hydroxybutyl)-4-methyl-1*H*-benzotriazol-5-yl]propanoate**

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Using General Procedure 8 starting from ethyl 3-(3-{[6-(benzyloxy)-2,2-dioxo-2*H*-1,2λ<sup>6</sup>,3-benzoxathiazin-3(4*H*)-yl]methyl}-4-chloro-5-methoxyphenyl)-3-(1-{4-[(4-methoxyphenyl)methoxy]butyl}-4-methyl-1*H*-benzotriazol-5-yl)propanoate (1 eq.) as a reactant, the title compound (97% yield) was obtained.

5 <sup>1</sup>H-NMR (400 MHz, DMSO-d<sub>6</sub>) δ ppm: 9.67 (s, 2 H), 7.62 (d, 1 H), 7.57 (d, 1 H), 7.12 (d, 1 H), 7.01 (dd, 1 H), 6.94 (d, 1 H), 6.78 (dd, 1 H), 6.6 (d, 1 H), 4.9 (t, 1 H), 4.64 (t, 2 H), 4.49 (s, 2 H), 4.4 (t, 1 H), 4.29 (m, 2 H), 3.93 (q, 2 H), 3.8 (t, 2 H), 3.39 (m, 3 H), 3.21 (d, 3 H), 2.79 (s, 2 H), 1.9 (m, 2 H), 1.37 (m, 2 H), 1 (t, 3 H)

10 **STEP 4 : Preparation of ethyl 3-[1-(4-bromobutyl)-4-methyl-1*H*-benzotriazol-5-yl]-3-{4-chloro-3-[(6-hydroxy-2,2-dioxo-2*H*-1,2λ<sup>6</sup>,3-benzoxathiazin-3(4*H*)-yl)methyl]-5-methoxyphenyl}propanoate**

Using General Procedure 9 starting from ethyl 3-{4-chloro-3-[(6-hydroxy-2,2-dioxo-2*H*-1,2λ<sup>6</sup>,3-benzoxathiazin-3(4*H*)-yl)methyl]-5-methoxyphenyl}-3-[1-(4-hydroxybutyl)-4-methyl-1*H*-benzotriazol-5-yl]propanoate (1 eq.) as a reactant, the title compound (76% yield) was obtained.

15 <sup>1</sup>H-NMR (400 MHz, DMSO-d<sub>6</sub>) δ ppm: 9.66 (s, 1 H), 7.65 (d, 1 H), 7.59 (d, 1 H), 7.14 (d, 1 H), 7.02 (d, 1 H), 6.95 (d, 1 H), 6.76 (dd, 1 H), 6.59 (d, 1 H), 4.89 (t, 1 H), 4.69 (t, 2 H), 4.48 (s, 2 H), 4.29 (m, 2 H), 3.95 (q, 2 H), 3.83 (s, 3 H), 3.53 (t, 2 H), 3.23 (d, 2 H), 2.8 (s, 3 H), 2 (m, 2 H), 1.77 (m, 2 H), 1.01 (t, 3 H)

25 **STEP 5 : Preparation of ethyl [4-chloro-5-methoxy-31-methyl-27,27-dioxo-21,26-dioxo-27λ<sup>6</sup>-thia-1,14,15,16-tetraazahexacyclo[20.5.3.1<sup>3,7</sup>.1<sup>9,13</sup>.0<sup>12,16</sup>.0<sup>25,29</sup>]dotriacont-3(32),4,6,9(31),10,12,14,22,24,29-decaen-8-yl]acetate**

Using General Procedure 11 starting from ethyl 3-[1-(4-bromobutyl)-4-methyl-1*H*-benzotriazol-5-yl]-3-{4-chloro-3-[(6-hydroxy-2,2-dioxo-2*H*-1,2λ<sup>6</sup>,3-benzoxathiazin-3(4*H*)-yl)methyl]-5-methoxyphenyl}propanoate (1 eq.) as a reactant, the title compound (72% yield) was obtained.

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<sup>1</sup>H-NMR (400 MHz, DMSO-d<sub>6</sub>) δ ppm: 7.69 (d, 1 H), 7.47 (d, 1 H), 7.44/6.31 (2d, 2 H), 6.98 (d, 1 H), 6.79 (dd, 1 H), 5.81 (d, 1 H), 4.85 (m, 1 H), 4.77 (m, 2 H), 4.23 (d, 4 H), 4.07-3.8 (m, 4 H), 3.98 (s, 3 H), 3.66/3.42 (m+dt, 2 H), 3.26/3.11 (2dd, 2 H), 2.65 (s, 3 H), 2.2/2.08 (2m, 2 H), 1.82/1.65 (2m, 2 H), 1.01 (t, 3 H)

5

**STEP 6 : Preparation of EXAMPLE 38**

Using General Procedure 12 starting from ethyl [4-chloro-5-methoxy-31-methyl-27,27-dioxo-21,26-dioxa-27λ<sup>6</sup>-thia-1,14,15,16-tetraazahexacyclo[20.5.3.1<sup>3,7</sup>.1<sup>9,13</sup>.0<sup>12,16</sup>.0<sup>25,29</sup>]dotriaconta-

10 3(32),4,6,9(31),10,12,14,22,24,29-decaen-8-yl]acetate (1 eq.) as a reactant, the title compound (white solid, 66% yield) was obtained.

The enantiopure products were obtained by chromatographic separation on chiral column.

**Example 38a (E1)**

15 **HRMS** calculated for C<sub>29</sub>H<sub>29</sub>ClN<sub>4</sub>O<sub>7</sub>S: 612.1445; [M+H]<sup>+</sup> found: 613.1522 (δ=0.6 ppm)

**Example 38b (E2)**

**HRMS** calculated for C<sub>29</sub>H<sub>29</sub>ClN<sub>4</sub>O<sub>7</sub>S: 612.1445; [M+H]<sup>+</sup> found: 613.1522 (δ=0.6 ppm)

<sup>1</sup>H-NMR (400 MHz, DMSO-d<sub>6</sub>) δ ppm: 12.3 (m, 1 H), 7.7 (d, 1 H), 7.5 (m, 2 H), 7 (d, 1 H),

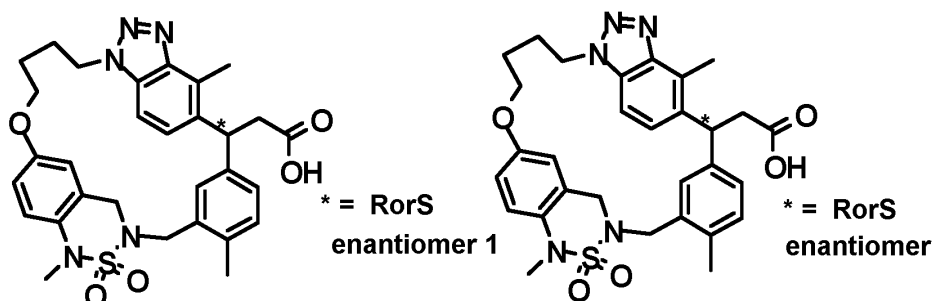
20 6.8 (dd, 1 H), 6.3 (d, 1 H), 5.8 (d, 1 H), 4.8 (m, 3 H), 4.25/3.95 (2d, 2 H), 4.1/3.8 (2d, 2 H), 4 (s, 3 H), 3.65/3.4 (m, 2 H), 3.15/3 (2dd, 2 H), 2.7 (sl, 3 H), 2.2/2.1 (2m, 2 H), 1.85/1.65 (m, 2 H)

**EXAMPLE 39** : [4,26,31-Trimethyl-27,27-dioxo-21-oxa-27λ<sup>6</sup>-thia-1,14,15,16,26-

25 pentaazahexacyclo[20.5.3.1<sup>3,7</sup>.1<sup>9,13</sup>.0<sup>12,16</sup>.0<sup>25,29</sup>]dotriaconta-

3(32),4,6,9(31),10,12,14,22,24,29-decaen-8-yl]acetic acid

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### STEP C1 : Preparation of [5-(benzyloxy)-2-nitrophenyl]methanol

- 5 3-(Hydroxymethyl)-4-nitrophenol (1 eq., 4.15 g, 24.5 mmol) was dissolved in DMF (75 mL), NaH (1.1 eq., 1.08 g, 27.0 mmol) was added and the mixture was stirred at RT for 15min. After cooling to 0°C, (bromomethyl)benzene (1 eq., 2.92 mL, 4.20 g, 24.6 mmol) was added dropwise and the reaction mixture was stirred at RT overnight. After completion of the reaction the mixture was concentrated under reduced pressure, the residue was treated with water, the
- 10 precipitated solid was filtered, washed with water and dried to give the title compound ( 5.77 g, 91% yield) as a yellowish solid, which was used in the next step without further purification.
- <sup>1</sup>H-NMR (500 MHz, DMSO-d<sub>6</sub>) δ ppm: 8.14 (d, 1 H), 7.52-7.31 (m, 5 H), 7.44 (d, 1 H), 7.11 (dd, 1 H), 5.59 (t, 1 H), 5.26 (s, 2 H), 4.85 (d, 2 H)

### 15 STEP C2 : Preparation of 2-{[5-(benzyloxy)-2-nitrophenyl]methyl}-1*H*-isoindole-1,3(2*H*)-dione

- [5-(Benzyloxy)-2-nitrophenyl]methanol (1 eq., 5.76g, 22.2 mmol) was dissolved in THF (250 mL), 1*H*-isoindole-1,3(2*H*)-dione (1 eq., 3.27g, 22.2 mmol) and PPh<sub>3</sub> (2 eq., 11.65g, 44.42 mmol) were added, and the solution was cooled to 5-10°C. DIAD (2 eq., 8.75 mL, 8.99g, 44.4 mmol) was added dropwise and the mixture was stirred at RT for 1h. After concentration under reduced pressure, the residue was purified via normal phase silica gel chromatography using DCM-MeOH (100:0 to 95:5) as eluents to give the title compound (2.89 g, 34% yield) as a yellowish white solid.



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<sup>1</sup>H-NMR (500 MHz, DMSO-d<sub>6</sub>) δ ppm: 8.21 (d, 1 H), 7.95-7.85 (m, 4 H), 7.37-7.25 (m, 5 H), 7.19 (dd, 1 H), 6.87 (d, 1 H), 5.17 (s, 2 H), 5.09 (s, 2 H)

**STEP C3 : Preparation of 1-[5-(benzyloxy)-2-nitrophenyl]methanamine**

5

2-{[5-(Benzyloxy)-2-nitrophenyl]methyl}-1*H*-isoindole-1,3(2*H*)-dione (1 eq., 2.89 g, 7.44 mmol) was dissolved in EtOH (6 mL). Hydrazine hydrate (5 eq., 1.81 mL, 1.86 g, 37.38 mmol) was added and the reaction mixture was stirred at 50°C overnight. After cooling to RT, the solid was filtered off and the mother liquor was concentrated under reduced pressure. The residue was dissolved in DCM, washed with sat. aq. NaHCO<sub>3</sub> solution, dried over MgSO<sub>4</sub>, filtered, concentrated under reduced pressure to give the title compound (1.86 g, 97% yield) as a yellowish oil, which was used in a next step without purification.

10

<sup>1</sup>H-NMR (500 MHz, DMSO-d<sub>6</sub>) δ ppm: 8.05 (d, 1 H), 7.5-7.32 (m, 5 H), 7.44 (d, 1 H), 7.07 (dd, 1 H), 5.25 (s, 2 H), 3.99 (s, 2 H), 1.96 (brs, 2 H)

15

**STEP C4 : Preparation of 2-(aminomethyl)-4-(benzyloxy)aniline**

1-[5-(Benzyloxy)-2-nitrophenyl]methanamine (1 eq., 1.86g, 7.20 mmol) was dissolved in EtOH (27 mL), then water (8 mL), iron powder (10 eq., 4.026 g, 72.09 mmol) and NH<sub>4</sub>Cl (0.5 eq., 193 mg, 3.6081 mmol) were added. The reaction mixture was refluxed for 1h. After cooling to RT, the mixture was filtered through a Celite pad and concentrated under reduced pressure. The residue was dissolved in EtOAc and washed with 1M aq. NaOH solution. The organic phase was dried over MgSO<sub>4</sub>, filtered, concentrated under reduced pressure to give the title compound (1.427 g, 87% yield) as a brownish oil, which was used in the next step without purification.

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<sup>1</sup>H-NMR (500 MHz, DMSO-d<sub>6</sub>) δ ppm: 7.44-7.27 (m, 5 H), 6.79 (d, 1 H), 6.63 (dd, 1 H), 6.53 (d, 1 H), 4.94 (s, 2 H), 3.57 (s, 2 H)

25

**STEP C5 : Preparation of 6-(benzyloxy)-3,4-dihydro-2*H*,1,3-benzothiadiazine-2,2(1*H*)-dione**

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2-(Aminomethyl)-4-(benzyloxy)aniline (1 eq., 1.42 g, 6.22 mmol) was dissolved in pyridine (45 mL). Sulfuric diamide (7 eq., 4.18 g, 43.5 mmol) was added and the mixture was refluxed for 2h. The reaction mixture was concentrated under reduced pressure and the residue was treated with 60 mL 0.5 M aq. HCl solution. The precipitated solid was filtered off, dried in vacuum to give the title compound (1.721 g, 95% yield) as yellowish white solid, which was used in the next step without purification.

<sup>1</sup>H-NMR (500 MHz, DMSO-d<sub>6</sub>) δ ppm: 9.82 (s, 1 H), 7.45-7.28 (m, 5 H), 7.17 (t, 1 H), 6.87 (dd, 1 H), 6.84 (d, 1 H), 6.65 (d, 1 H), 5.03 (s, 2 H), 4.36 (d, 2 H)

10 **STEP C6 : Preparation of 6-(benzyloxy)-1-methyl-3,4-dihydro-2λ<sup>6</sup>,1,3-benzothiadiazine-2,2(1H)-dione**

6-(Benzyloxy)-3,4-dihydro-2λ<sup>6</sup>,1,3-benzothiadiazine-2,2(1H)-dione (1 eq., 1.57 g, 5.41 mmol) was dissolved in THF (50 mL). PPh<sub>3</sub> (2 eq., 2.83 g, 10.82 mmol) and MeOH (1.1 eq., 0.24 mL, 190 mg, 5.925 mmol) were added. The reaction mixture was cooled to 0°C, and DIAD (2 eq., 2.13 mL, 2.19 g, 10.8 mmol) was added dropwise into the stirred reaction mixture at 0°C, followed by stirring at this temperature for 2h. The reaction mixture was concentrated under reduced pressure, the residue was purified via flash chromatography using DCM as eluent to give the title compound (690 mg, 42% yield) as a white solid.

20 <sup>1</sup>H-NMR (500 MHz, DMSO-d<sub>6</sub>) δ ppm: 7.69 (brs, 1 H), 7.46-7.29 (m, 5 H), 6.98 (d, 1 H), 6.94 (dd, 1 H), 6.87 (d, 1 H), 5.07 (s, 2 H), 4.38 (s, 2 H), 3.12 (s, 3 H)

25 **STEP 1 : Preparation of ethyl 3-{1-[4-(benzyloxy)butyl]-4-methyl-1H-benzotriazol-5-yl}-3-(3-{[6-(benzyloxy)-1-methyl-2,2-dioxo-1,4-dihydro-2λ<sup>6</sup>,1,3-benzothiadiazin-3(2H)-yl]methyl}-4-methylphenyl)propanoate**

Using General Procedure 7 starting from ethyl 3-{1-[4-(benzyloxy)butyl]-4-methyl-1H-benzotriazol-5-yl}-3-[3-(hydroxymethyl)-4-methylphenyl]propanoate (1 eq.) and 6-(benzyloxy)-1-methyl-3,4-dihydro-2λ<sup>6</sup>,1,3-benzothiadiazine-2,2(1H)-dione (1 eq.) as reactants, the title compound (57% yield) was obtained.

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<sup>1</sup>H-NMR (500 MHz, DMSO-d<sub>6</sub>) δ ppm: 7.57 (d, 1 H), 7.47 (d, 1 H), 7.45 (d, 2 H), 7.39 (t, 2 H), 7.33 (t, 1 H), 7.3 (t, 2 H), 7.25 (d, 2 H), 7.24 (t, 1 H), 7.19 (dd, 1 H), 7.13 (d, 1 H), 7.12 (d, 1 H), 7.08 (d, 1 H), 7.03 (dd, 1 H), 6.82 (d, 1 H), 5.09 (s, 2 H), 4.84 (t, 1 H), 4.61 (t, 2 H), 4.38 (s, 2 H), 4.27 (s, 2 H), 4.01 (s, 2 H), 3.91 (q, 2 H), 3.38 (t, 2 H), 3.24 (s, 3 H), 3.19/3.14 (dd+dd, 2 H), 2.75 (s, 3 H), 2.21 (s, 3 H), 1.9 (qn, 2 H), 1.46 (qn, 2 H), 0.97 (t, 3 H)

**STEP 2 : Preparation of ethyl 3-[1-(4-hydroxybutyl)-4-methyl-1*H*-benzotriazol-5-yl]-3-{3-[(6-hydroxy-1-methyl-2,2-dioxo-1,4-dihydro-2λ<sup>6</sup>,1,3-benzothiadiazin-3(2*H*)-yl)methyl]-4-methylphenyl}propanoate**

10

Using General Procedure 8 starting from ethyl 3-{1-[4-(benzyloxy)butyl]-4-methyl-1*H*-benzotriazol-5-yl]-3-(3-{[6-(benzyloxy)-1-methyl-2,2-dioxo-1,4-dihydro-2λ<sup>6</sup>,1,3-benzothiadiazin-3(2*H*)-yl)methyl]-4-methylphenyl}propanoate (1 eq.) as a reactant, the title compound (quant.) was obtained.

<sup>1</sup>H-NMR (500 MHz, DMSO-d<sub>6</sub>) δ ppm: 9.42 (s, 1 H), 7.61 (d, 1 H), 7.5 (d, 1 H), 7.19 (dd, 1 H), 7.13 (brs., 1 H), 7.12 (d, 1 H), 6.96 (d, 1 H), 6.76 (dd, 1 H), 6.49 (d, 1 H), 4.83 (t, 1 H), 4.64 (t, 2 H), 4.43 (t, 1 H), 4.23/4.19 (d+d, 2 H), 4.04/3.99 (d+d, 2 H), 3.93 (q, 2 H), 3.38 (q, 2 H), 3.19 (s, 3 H), 3.16 (m, 2 H), 2.74 (s, 3 H), 2.22 (s, 3 H), 1.9 (m, 2 H), 1.36 (m, 2 H), 0.99 (t, 3 H)

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**STEP 3 : Preparation of ethyl 3-[1-(4-chlorobutyl)-4-methyl-1*H*-benzotriazol-5-yl]-3-{3-[(6-hydroxy-1-methyl-2,2-dioxo-1,4-dihydro-2λ<sup>6</sup>,1,3-benzothiadiazin-3(2*H*)-yl)methyl]-4-methylphenyl}propanoate hydrochloride**

Using General Procedure 10 starting from ethyl 3-[1-(4-hydroxybutyl)-4-methyl-1*H*-benzotriazol-5-yl]-3-{3-[(6-hydroxy-1-methyl-2,2-dioxo-1,4-dihydro-2λ<sup>6</sup>,1,3-benzothiadiazin-3(2*H*)-yl)methyl]-4-methylphenyl}propanoate (1 eq.) as a reactant, the title compound (quant.) was obtained.

<sup>1</sup>H-NMR (500 MHz, DMSO-d<sub>6</sub>) δ ppm: 9.43 (br., 1 H), 7.64 (d, 1 H), 7.51 (d, 1 H), 7.19 (dd, 1 H), 7.13 (d, 1 H), 7.12 (d, 1 H), 6.96 (d, 1 H), 6.77 (dd, 1 H), 6.49 (d, 1 H), 4.83 (t, 1 H), 4.69

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(t, 2 H), 4.23/4.19 (d+d, 2 H), 4.04/3.99 (d+d, 2 H), 3.93 (q, 2 H), 3.64 (t, 2 H), 3.19 (s, 3 H), 3.17 (m, 2 H), 2.74 (s, 3 H), 2.22 (s, 3 H), 1.99 (m, 2 H), 1.68 (m, 2 H), 0.99 (t, 3 H)

**STEP 4 : Preparation of ethyl [4,26,31-trimethyl-27,27-dioxo-21-oxa-27 $\lambda^6$ -thia-1,14,15,16,26-pentaazahexacyclo[20.5.3.1<sup>3,7</sup>.1<sup>9,13</sup>.0<sup>12,16</sup>.0<sup>25,29</sup>]dotriaconta-3(32),4,6,9(31),10,12,14,22,24,29-decaen-8-yl]acetate**

Using General Procedure 11 starting from ethyl 3-[1-(4-chlorobutyl)-4-methyl-1*H*-benzotriazol-5-yl]-3-{3-[(6-hydroxy-1-methyl-2,2-dioxo-1,4-dihydro-2 $\lambda^6$ ,1,3-benzothiadiazin-3(2*H*)-yl)methyl]-4-methylphenyl}propanoate hydrochloride (1 eq.) as a reactant, the title compound (quant.) was obtained.

**<sup>1</sup>H-NMR** (500 MHz, DMSO-*d*<sub>6</sub>)  $\delta$  ppm: 7.68 (d, 1 H), 7.45 (d, 1 H), 7.45 (d, 1 H), 7.26 (d, 1 H), 6.94 (d, 1 H), 6.76 (dd, 1 H), 6.51 (d, 1 H), 5.71 (d, 1 H), 4.78 (t, 1 H), 4.76 (m, 2 H), 3.95/3.76 (d+d, 2 H), 3.92 (q, 2 H), 3.9/3.76 (d+d, 2 H), 3.62/3.42 (m+m, 2 H), 3.18 (s, 3 H), 3.16/3.05 (dd+dd, 2 H), 2.61 (s, 3 H), 2.33 (s, 3 H), 2.19/2.09 (m+m, 2 H), 1.82/1.64 (m+m, 2 H), 1 (t, 3 H)

**STEP 5 : Preparation of EXAMPLE 39**

Using General Procedure 12 starting from ethyl [4,26,31-trimethyl-27,27-dioxo-21-oxa-27 $\lambda^6$ -thia-1,14,15,16,26-pentaazahexacyclo[20.5.3.1<sup>3,7</sup>.1<sup>9,13</sup>.0<sup>12,16</sup>.0<sup>25,29</sup>]dotriaconta-3(32),4,6,9(31),10,12,14,22,24,29-decaen-8-yl]acetate (1 eq.) as a reactant, the title compound (white solid, 55% yield) was obtained.

The enantiopure products were obtained by chromatographic separation on chiral column.

25

**Example 39a (E1, optical purity>99.9%)**

**HRMS** calculated for C<sub>30</sub>H<sub>33</sub>N<sub>5</sub>O<sub>5</sub>S: 575.2202; [M+H]<sup>+</sup> found: 576.2273 ( $\delta$  = -0.4 ppm)

**Example 39b (E2, optical purity~99.7%)**

**HRMS** calculated for C<sub>30</sub>H<sub>33</sub>N<sub>5</sub>O<sub>5</sub>S: 575.2202; [M+H]<sup>+</sup> found: 576.2252 ( $\delta$  = -4.0 ppm)

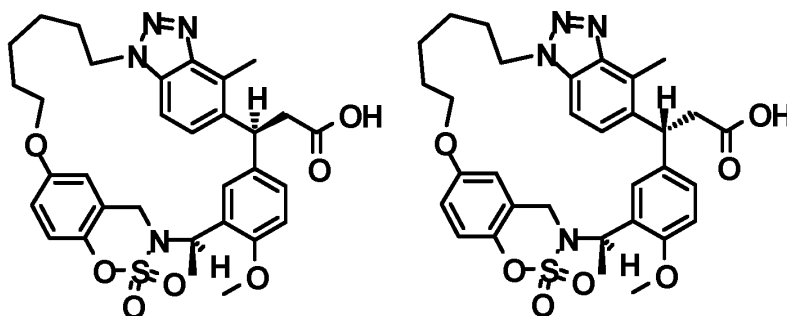
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**<sup>1</sup>H-NMR** (500 MHz, DMSO-d<sub>6</sub>) δ ppm: 7.67 (d, 1 H), 7.46 (dd, 1 H), 7.43 (d, 1 H), 7.26 (d, 1 H), 6.94 (d, 1 H), 6.76 (dd, 1 H), 6.49 (d, 1 H), 5.7 (d, 1 H), 4.76 (t, 1 H), 4.75 (m, 2 H), 3.94/3.76 (d+d, 2 H), 3.9/3.76 (d+d, 2 H), 3.61/3.4 (m+m, 2 H), 3.18 (s, 3 H), 3.04/2.94 (dd+dd, 2 H), 2.6 (s, 3 H), 2.33 (s, 3 H), 2.2/2.11 (m+m, 2 H), 1.82/1.64 (m+m, 2 H)

**<sup>13</sup>C-NMR** (125 MHz, DMSO-d<sub>6</sub>) δ ppm: 131.2, 130.8, 128.2, 127.4, 118.2, 116.3, 111.8, 108, 67.6, 51.1, 49.6, 48.3, 41.8, 41, 33.6, 26.7, 25.6, 18.6, 13.4

**EXAMPLE 40 :** [(2*R*,8*S*)-4-methoxy-2,33-dimethyl-29,29-dioxo-23,28-dioxa-29λ<sup>6</sup>-thia-1,14,15,16-tetraazahexacyclo[22.5.3.1<sup>3,7</sup>.1<sup>9,13</sup>.0<sup>12,16</sup>.0<sup>27,31</sup>]tetratriaconta-3(34),4,6,9(33),10,12,14,24,26,31-decaen-8-yl]acetic acid and [(2*R*,8*R*)-4-methoxy-2,33-dimethyl-29,29-dioxo-23,28-dioxa-29λ<sup>6</sup>-thia-1,14,15,16-tetraazahexacyclo[22.5.3.1<sup>3,7</sup>.1<sup>9,13</sup>.0<sup>12,16</sup>.0<sup>27,31</sup>]tetratriaconta-3(34),4,6,9(33),10,12,14,24,26,31-decaen-8-yl]acetic acid



**STEP 1 : Preparation of ethyl 3-{1-[6-(benzyloxy)hexyl]-4-methyl-1*H*-benzotriazol-5-yl}-3-{3-[(1*S*)-1-hydroxyethyl]-4-methoxyphenyl}propanoate**

Using General Procedure 6 starting from ethyl (E)-3-[1-(6-benzyloxyhexyl)-4-methyl-benzotriazol-5-yl]prop-2-enoate (1 eq.) and (1*S*)-1-[2-methoxy-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]ethanol (1.1 eq.) as reactants, the title compound (50% yield) was obtained.

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<sup>1</sup>H-NMR (400 MHz, DMSO-d<sub>6</sub>) δ ppm: 7.6 (d, 1 H), 7.48 (d, 1 H), 7.38 (d, 1 H), 7.32-7.25 (m, 5 H), 7.11 (dd, 1 H), 6.81 (d, 1 H), 4.9 (d, 1 H), 4.9 (m, 1 H), 4.8 (m, 1 H), 4.62 (t, 2 H), 4.4 (s, 2 H), 3.91 (q, 2 H), 3.71 (s, 3 H), 3.38 (t, 2 H), 3.1 (d, 2 H), 2.78 (s, 3 H), 1.88 (m, 2 H), 1.5 (m, 2 H), 1.35 (m, 2 H), 1.2 (m+d, 5 H), 1 (t, 3 H)

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**STEP 2 : Preparation of ethyl 3-(3-((1*R*)-1-[6-(benzyloxy)-2,2-dioxo-2*H*-1,2λ<sup>6</sup>,3-benzoxathiazin-3(4*H*)-yl]ethyl)-4-methoxyphenyl)-3-{1-[6-(benzyloxy)hexyl]-4-methyl-1*H*-benzotriazol-5-yl}propanoate**

10 Using General Procedure 7 starting from ethyl 3-{1-[6-(benzyloxy)hexyl]-4-methyl-1*H*-benzotriazol-5-yl}-3-{3-[(1*S*)-1-hydroxyethyl]-4-methoxyphenyl}propanoate (1 eq.) and 6-(benzyloxy)-3,4-dihydro-2*H*-1,2λ<sup>6</sup>,3-benzoxathiazine-2,2-dione (1.5 eq.) as reactants, the title compound (beige solid, 71% yield) was obtained.

<sup>1</sup>H-NMR (400 MHz, DMSO-d<sub>6</sub>) δ ppm: 0.97 (t, J=7.09 Hz, 5 H) 1.10 - 1.26 (m, 7 H) 1.29 (br. s., 3 H) 1.37 - 1.53 (m, 7 H) 1.75 - 1.91 (m, 3 H) 2.72 - 2.79 (m, 4 H) 3.09 - 3.21 (m, 3 H) 3.33 - 3.41 (m, 3 H) 3.64 (d, J=1.71 Hz, 3 H) 3.91 (qd, J=6.95, 2.26 Hz, 2 H) 4.38 (d, J=1.47 Hz, 2 H) 4.46 - 4.65 (m, 3 H) 4.82 (q, J=8.15 Hz, 1 H) 4.86 - 5.12 (m, 2 H) 5.28 - 5.45 (m, 1 H) 6.63 - 6.82 (m, 2 H) 6.82 - 6.97 (m, 2 H) 7.08 - 7.48 (m, 12 H) 7.48 - 7.55 (m, 1 H) 7.57 - 7.68 (m, 1 H)

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**STEP 3 : Preparation of ethyl 3-{3-[(1*R*)-1-(6-hydroxy-2,2-dioxo-2*H*-1,2λ<sup>6</sup>,3-benzoxathiazin-3(4*H*)-yl)ethyl]-4-methoxyphenyl}-3-[1-(6-hydroxyhexyl)-4-methyl-1*H*-benzotriazol-5-yl]propanoate**

25 Using General Procedure 8 starting from ethyl 3-(3-((1*R*)-1-[6-(benzyloxy)-2,2-dioxo-2*H*-1,2λ<sup>6</sup>,3-benzoxathiazin-3(4*H*)-yl]ethyl)-4-methoxyphenyl)-3-{1-[6-(benzyloxy)hexyl]-4-methyl-1*H*-benzotriazol-5-yl}propanoate (1 eq.) as a reactant, the title compound (98% yield) was obtained.

<sup>1</sup>H-NMR (400 MHz, DMSO-d<sub>6</sub>) δ ppm: 0.91 - 1.04 (m, 7 H) 1.11 - 1.47 (m, 23 H) 1.87 (quint, J=7.12 Hz, 4 H) 2.73 - 2.78 (m, 5 H) 3.13 - 3.22 (m, 3 H) 3.32 - 3.36 (m, 3 H) 3.57 - 3.59 (m, 3

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H) 3.67 (d, J=0.98 Hz, 6 H) 3.94 (q, J=7.46 Hz, 4 H) 4.29 (t, J=5.07 Hz, 2 H) 4.37 - 4.57 (m, 3 H) 4.63 (t, J=6.91 Hz, 4 H) 4.78 - 4.87 (m, 2 H) 5.37 (quint, J=7.06 Hz, 2 H) 6.51 (dd, J=12.35, 2.81 Hz, 2 H) 6.64 (dd, J=8.80, 2.69 Hz, 2 H) 6.76 (d, J=1.22 Hz, 1 H) 6.77 - 6.84 (m, 1 H) 7.13 (dd, J=8.56, 1.96 Hz, 1 H) 7.42 (dd, J=11.13, 2.08 Hz, 1 H) 7.53 (t, J=9.05 Hz, 1 H) 7.59 - 7.66 (m, 1 H) 9.52 (d, J=3.55 Hz, 1 H)

**STEP 4 : Preparation of ethyl 3-[1-(6-bromohexyl)-4-methyl-1*H*-benzotriazol-5-yl]-3-{3-[(1*R*)-1-(6-hydroxy-2,2-dioxo-2*H*-1,2λ<sup>6</sup>,3-benzoxathiazin-3(4*H*)-yl)ethyl]-4-methoxyphenyl}propanoate**

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Using General Procedure 9 starting from ethyl 3-{3-[(1*R*)-1-(6-hydroxy-2,2-dioxo-2*H*-1,2λ<sup>6</sup>,3-benzoxathiazin-3(4*H*)-yl)ethyl]-4-methoxyphenyl}-3-[1-(6-hydroxyhexyl)-4-methyl-1*H*-benzotriazol-5-yl]propanoate (1 eq.) as a reactant, the title compound (77% yield) was obtained.

**<sup>1</sup>H-NMR** (400 MHz, DMSO-d<sub>6</sub>) δ ppm: 9.5 (s, 1 H), 7.6 (d, 1 H), 7.55 (d, 1 H), 7.4 (d, 1 H), 7.1 (m, 1 H), 6.8 (m, 1 H), 6.75 (d, 1 H), 6.65 (d, 1 H), 6.5 (d, 1 H), 5.4 (m, 1 H), 4.8 (m, 1 H), 4.65 (t, 2 H), 4.5 (m, 2 H), 3.95 (q, 2 H), 3.7 (s, 3 H), 3.45 (t, 2 H), 3.2 (m, 2 H), 2.75 (d, 3 H), 1.9 (quint, 2 H), 1.75 (quint, 2 H), 1.4 (t, 3 H), 1.4/1.25 (2m, 4 H), 1 (m, 3 H)

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**STEP 5 : Preparation of ethyl [(2*R*)-4-methoxy-2,33-dimethyl-29,29-dioxo-23,28-dioxo-29λ<sup>6</sup>-thia-1,14,15,16-tetraazahexacyclo[22.5.3.1<sup>3,7</sup>.1<sup>9,13</sup>.0<sup>12,16</sup>.0<sup>27,31</sup>]tetratriaconta-3(34),4,6,9(33),10,12,14,24,26,31-decaen-8-yl]acetate**

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Using General Procedure 11 starting from ethyl 3-[1-(6-bromohexyl)-4-methyl-1*H*-benzotriazol-5-yl]-3-{3-[(1*R*)-1-(6-hydroxy-2,2-dioxo-2*H*-1,2λ<sup>6</sup>,3-benzoxathiazin-3(4*H*)-yl)ethyl]-4-methoxyphenyl}propanoate (1 eq.) as a reactant, the title compound (65% yield) was obtained.

25

**<sup>1</sup>H-NMR** (400 MHz, DMSO-d<sub>6</sub>) δ ppm: 0.93 - 1.03 (m, 8 H) 1.24 (d, J=4.65 Hz, 8 H) 1.32 - 1.67 (m, 15 H) 1.96 (d, J=6.85 Hz, 4 H) 2.85 (s, 7 H) 2.97 - 3.12 (m, 3 H) 3.15 - 3.22 (m, 3 H) 3.39 - 3.48 (m, 1 H) 3.62 (d, J=18.71 Hz, 8 H) 3.67 - 3.78 (m, 2 H) 3.91 (qd, J=7.05, 5.01 Hz, 5

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H) 4.10 - 4.27 (m, 2 H) 4.24 - 4.38 (m, 3 H) 4.59 - 4.74 (m, 6 H) 4.79 - 4.90 (m, 3 H) 5.42 (q, J=7.17 Hz, 1 H) 5.51 (q, J=7.13 Hz, 1 H) 5.86 (d, J=2.81 Hz, 1 H) 6.24 (d, J=2.81 Hz, 1 H) 6.72 (d, J=8.56 Hz, 4 H) 6.84 (d, J=8.56 Hz, 1 H) 6.90 (dd, J=9.05, 4.16 Hz, 2 H) 7.12 - 7.25 (m, 2 H) 7.36 (d, J=8.80 Hz, 1 H) 7.46 (dd, J=8.56, 2.08 Hz, 1 H) 7.57 - 7.73 (m, 5 H)

5

**STEP 6 : Preparation of EXAMPLE 40**

Using General Procedure 12 starting from ethyl [(2*R*)-4-methoxy-2,33-dimethyl-29,29-dioxo-23,28-dioxa-29λ<sup>6</sup>-thia-1,14,15,16-tetraazahexacyclo[22.5.3.1<sup>3,7</sup>.1<sup>9,13</sup>.0<sup>12,16</sup>.0<sup>27,31</sup>]tetratriaconta-

10 3(34),4,6,9(33),10,12,14,24,26,31-decaen-8-yl]acetate (1 eq.) as a reactant, the title compound (white solid, 79% yield) was obtained.

The diastereo-pure products were obtained by chromatographic separation on chiral column.

**Example 40a (2*R*,8*S*)**

15 **HRMS** calculated for C<sub>32</sub>H<sub>36</sub>N<sub>4</sub>O<sub>7</sub>S: 620.2305; [M+H]<sup>+</sup> found: 621.2378 (δ=0.1 ppm)

**<sup>1</sup>H-NMR** (400 MHz, DMSO-d<sub>6</sub>) δ ppm: 12.1 (m, 1 H), 7.62 (d, 1 H), 7.46 (dd, 1 H), 7.31 (d, 1 H), 7.15 (d, 1 H), 6.91 (d, 1 H), 6.87 (d, 1 H), 6.72 (dd, 1 H), 5.87 (d, 1 H), 5.42 (q, 1 H), 4.84 (t, 1 H), 4.67 (m, 2 H), 4.16 (dd, 2 H), 3.66 (s, 3 H), 3.61/3.46 (2m, 2 H), 3.01/2.91 (2dd, 2 H), 2.85 (s, 3 H), 1.97 (m, 2 H), 1.68-1.16 (m, 6 H), 1.35 (d, 3 H)

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**Example 40b (2*R*,8*R*)**

**HRMS** calculated for C<sub>32</sub>H<sub>36</sub>N<sub>4</sub>O<sub>7</sub>S: 620.2305; [M+H]<sup>+</sup> found: 621.2377 (δ=-0.1 ppm)

**<sup>1</sup>H-NMR** (400 MHz, DMSO-d<sub>6</sub>) δ ppm: 12.08 (m, 1 H), 7.66 (d, 1 H), 7.59 (d, 1 H), 7.58 (d, 1 H), 7.2 (dd, 1 H), 6.9 (d, 1 H), 6.73 (d, 1 H), 6.72 (dd, 1 H), 6.24 (d, 1 H), 5.51 (q, 1 H), 4.82 (t, 1 H), 4.67 (m, 2 H), 4.29 (dd, 2 H), 3.65 (s, 3 H), 3.6/3.5 (2m, 2 H), 3.07 (d, 2 H), 2.84 (s, 3 H), 1.96 (m, 2 H), 1.7-1.2 (m, 6 H), 1.54 (d, 3 H)

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**EXAMPLE 41 :** [(2*R*,8*S*)-4-Methoxy-2,32-dimethyl-28,28-dioxo-19,22,27-trioxa-28λ<sup>6</sup>-thia-1,14,15,16-tetraazahexacyclo[21.5.3.1<sup>3,7</sup>.1<sup>9,13</sup>.0<sup>12,16</sup>.0<sup>26,30</sup>]tritrtriaconta-

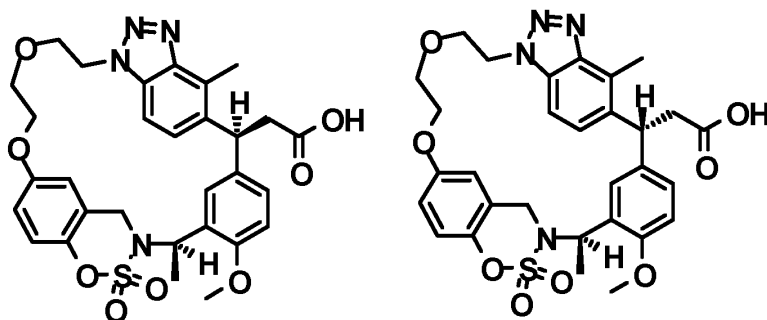
30

3(33),4,6,9(32),10,12,14,23,25,30-decaen-8-yl]acetic acid and



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[(2*R*,8*R*)-4-methoxy-2,32-dimethyl-28,28-dioxo-19,22,27-trioxa-28 $\lambda^6$ -thia-1,14,15,16-tetraazahexacyclo[21.5.3.1<sup>3,7</sup>.1<sup>9,13</sup>.0<sup>12,16</sup>.0<sup>26,30</sup>]tritriacont-3(33),4,6,9(32),10,12,14,23,25,30-decaen-8-yl]acetic acid



5

**STEP 1 : Preparation of ethyl 3-(1-{2-[2-(benzyloxy)ethoxy]ethyl}-4-methyl-1*H*-benzotriazol-5-yl)-3-{3-[(1*S*)-1-hydroxyethyl]-4-methoxyphenyl}propanoate**

10 Using General Procedure 6 starting from ethyl (2*E*)-3-(1-{2-[2-(benzyloxy)ethoxy]ethyl}-4-methyl-1*H*-benzotriazol-5-yl)prop-2-enoate (1 eq.) and (1*S*)-1-[2-methoxy-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]ethan-1-ol (2 eq.) as reactants, the title compound (colorless oil, 52% yield) was obtained.

<sup>1</sup>H-NMR (400 MHz, DMSO-*d*<sub>6</sub>)  $\delta$  ppm 7.6 (d, 1 H), 7.45 (d, 1 H), 7.38 (s, 1 H), 7.3-7.2 (t+d, 5 H), 7.1 (d, 1 H), 6.8 (d, 1 H), 4.9 (d, 1 H), 4.9 (m, 1 H), 4.8 (t, 2 H), 4.8 (t, 1 H), 4.3 (s, 2 H), 3.9 (t, 2 H), 3.9 (q, 2 H), 3.7 (s, 3 H), 3.55/3.45 (t, 4 H), 3.1 (m, 2 H), 2.75 (s, 3 H), 1.2 (d, 3 H), 1 (t, 3 H)

20 **STEP 2 : Preparation of ethyl 3-(3-{(1*R*)-1-[6-(benzyloxy)-2,2-dioxo-2*H*-1,2 $\lambda^6$ ,3-benzoxathiazin-3(4*H*)-yl]ethyl}-4-methoxyphenyl)-3-(1-{2-[2-(benzyloxy)ethoxy]ethyl}-4-methyl-1*H*-benzotriazol-5-yl)propanoate**

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Using General Procedure 7 starting from ethyl 3-(1-{2-[2-(benzyloxy)ethoxy]ethyl}-4-methyl-1*H*-benzotriazol-5-yl)-3-{3-[(1*R*)-1-hydroxyethyl]-4-methoxyphenyl}propanoate (1 eq.) and 6-(benzyloxy)-3,4-dihydro-2*H*-1,2λ<sup>6</sup>,3-benzoxathiazine-2,2-dione (1.1 eq.) as reactants, the title compound (67% yield) was obtained.

- 5 <sup>1</sup>H-NMR (400 MHz, DMSO-d<sub>6</sub>) δ ppm: 7.63-7.45 (dd, 2 H), 7.45-7.05 (m, 12 H), 6.94-6.71 (m, 4 H), 5.36 (m, 1 H), 5.08-4.97 (dd, 2 H), 4.86-4.75 (m, 3 H), 4.54/4.51 (dd, 2 H), 4.29 (s, 2 H), 3.95-3.84 (m, 4 H), 3.63/3.62 (s, 3 H), 3.5/3.4 (m, 4 H), 3.17-3.1 (m, 2 H), 2.75/2.74 (s, 3 H), 1.42/1.4 (d, 3 H), 0.98 (t, 3 H)

10 **STEP 3 : Preparation of ethyl 3-{3-[(1*R*)-1-(6-hydroxy-2,2-dioxo-2*H*-1,2λ<sup>6</sup>,3-benzoxathiazin-3(4*H*)-yl)ethyl]-4-methoxyphenyl}-3-{1-[2-(2-hydroxyethoxy)ethyl]-4-methyl-1*H*-benzotriazol-5-yl}propanoate**

- Using General Procedure 8 starting from ethyl 3-(3-{(1*R*)-1-[6-(benzyloxy)-2,2-dioxo-2*H*-1,2λ<sup>6</sup>,3-benzoxathiazin-3(4*H*)-yl]ethyl}-4-methoxyphenyl)-3-(1-{2-[2-(benzyloxy)ethoxy]ethyl}-4-methyl-1*H*-benzotriazol-5-yl)propanoate (1 eq.) as a reactant, the title compound (white solid, 69% yield) was obtained.

- 15 <sup>1</sup>H-NMR (400 MHz, DMSO-d<sub>6</sub>) δ ppm: 0.96 - 1.05 (m, 3 H) 1.42 (t, J=6.64 Hz, 3 H) 2.76 (d, J=5.65 Hz, 3 H) 3.11 - 3.21 (m, 2 H) 3.38 (d, J=2.29 Hz, 4 H) 3.67 (s, 3 H) 3.85 - 3.91 (m, 2 H) 3.94 (qd, J=7.12, 1.22 Hz, 2 H) 4.38 - 4.57 (m, 3 H) 4.76 - 4.88 (m, 3 H) 5.37 (quin, J=7.02 Hz, 1 H) 6.51 (dd, J=16.02, 2.90 Hz, 1 H) 6.65 (dd, J=8.85, 2.90 Hz, 1 H) 6.75 - 6.84 (m, 2 H) 7.13 (dd, J=8.54, 1.83 Hz, 1 H) 7.43 (dd, J=8.54, 1.98 Hz, 1 H) 7.49 - 7.58 (m, 1 H) 7.61 - 7.68 (m, 1 H) 9.53 (br. s., 1 H)

25 **STEP 4 : Preparation of ethyl 3-{1-[2-(2-bromoethoxy)ethyl]-4-methyl-1*H*-benzotriazol-5-yl}-3-{3-[(1*R*)-1-(6-hydroxy-2,2-dioxo-2*H*-1,2λ<sup>6</sup>,3-benzoxathiazin-3(4*H*)-yl)ethyl]-4-methoxyphenyl}propanoate**

- Using General Procedure 9 starting from ethyl 3-{3-[(1*R*)-1-(6-hydroxy-2,2-dioxo-2*H*-1,2λ<sup>6</sup>,3-benzoxathiazin-3(4*H*)-yl)ethyl]-4-methoxyphenyl}-3-{1-[2-(2-hydroxyethoxy)ethyl]-4-

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methyl-1*H*-benzotriazol-5-yl}propanoate (1 eq.) as a reactant, the title compound (white solid, 94% yield) was obtained.

**<sup>1</sup>H-NMR** (400 MHz, DMSO-d<sub>6</sub>) δ ppm: 1.01 (td, J=7.09, 3.91 Hz, 3 H) 1.41 (t, J=6.54 Hz, 3 H) 2.75 (d, J=4.77 Hz, 3 H) 3.08 - 3.26 (m, 2 H) 3.45 (t, J=5.99 Hz, 2 H) 3.64 - 3.69 (m, 4 H) 3.88 - 3.98 (m, 6 H) 4.36 - 4.59 (m, 2 H) 4.76 - 4.87 (m, 3 H) 5.31 - 5.42 (m, 1 H) 6.51 (dd, J=11.13, 2.81 Hz, 1 H) 6.65 (dd, J=8.86, 2.87 Hz, 1 H) 6.75 - 6.85 (m, 2 H) 7.12 (dd, J=8.50, 1.90 Hz, 1 H) 7.42 (dd, J=7.03, 2.02 Hz, 1 H) 7.50 - 7.58 (m, 1 H) 7.62 - 7.68 (m, 1 H)

**STEP 5 : Preparation of ethyl [(2*R*)-4-methoxy-2,32-dimethyl-28,28-dioxo-19,22,27-trioxa-28λ<sup>6</sup>-thia-1,14,15,16-tetraazahexacyclo[21.5.3.1<sup>3,7</sup>.1<sup>9,13</sup>.0<sup>12,16</sup>.0<sup>26,30</sup>]tritiaconta-3(33),4,6,9(32),10,12,14,23,25,30-decaen-8-yl]acetate**

Using General Procedure 11 starting from ethyl 3-{1-[2-(2-bromoethoxy)ethyl]-4-methyl-1*H*-benzotriazol-5-yl}-3-{3-[(1*R*)-1-(6-hydroxy-2,2-dioxo-2*H*-1,2λ<sup>6</sup>,3-benzoxathiazin-3(4*H*)-yl)ethyl]-4-methoxyphenyl}propanoate (1 eq.) as a reactant, the title compound (white solid, 96% yield) was obtained.

**<sup>1</sup>H-NMR** (400 MHz, DMSO-d<sub>6</sub>) δ ppm: 1.01 (dt, J=17.58, 7.11 Hz, 7 H) 1.36 (d, J=7.09 Hz, 3 H) 1.61 (d, J=7.09 Hz, 4 H) 2.86 (d, J=4.89 Hz, 7 H) 2.93 - 3.12 (m, 3 H) 3.12 - 3.27 (m, 3 H) 3.45 - 3.64 (m, 8 H) 3.68 - 3.85 (m, 8 H) 3.86 - 3.98 (m, 10 H) 4.04 (d, J=11.13 Hz, 1 H) 4.08 - 4.26 (m, 3 H) 4.53 (d, J=17.85 Hz, 1 H) 4.74 - 4.97 (m, 9 H) 5.43 (q, J=6.77 Hz, 1 H) 5.56 (q, J=7.21 Hz, 1 H) 5.68 (d, J=2.57 Hz, 1 H) 6.45 (d, J=2.45 Hz, 1 H) 6.54 (d, J=8.56 Hz, 1 H) 6.60 (dd, J=8.93, 2.93 Hz, 1 H) 6.68 - 6.78 (m, 2 H) 6.85 (dd, J=11.19, 8.99 Hz, 3 H) 7.10 (s, 1 H) 7.13 (d, J=8.68 Hz, 1 H) 7.27 (d, J=8.80 Hz, 1 H) 7.45 (d, J=8.44 Hz, 1 H) 7.55 - 7.61 (m, 2 H) 7.70 (d, J=8.68 Hz, 1 H)

**STEP 6 : Preparation of EXAMPLE 41**

Using General Procedure 12 starting from ethyl [(2*R*)-4-methoxy-2,32-dimethyl-28,28-dioxo-19,22,27-trioxa-28λ<sup>6</sup>-thia-1,14,15,16-tetraazahexacyclo[21.5.3.1<sup>3,7</sup>.1<sup>9,13</sup>.0<sup>12,16</sup>.0<sup>26,30</sup>]

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tritriaconta-3(33),4,6,9(32),10,12,14,23,25,30-decaen-8-yl]acetate (1 eq.) as a reactant, the title compound (white solid, 72% yield) was obtained.

The diastereo-pure products were obtained by chromatographic separation on chiral column.

#### 5 **Example 41a (2R,8S)**

**HRMS** calculated for  $C_{30}H_{32}N_4O_8S$ : 608.1941;  $[M+H]^+$  found: 609.2014 ( $\delta=0.1$  ppm)

**$^1H$ -NMR** (400 MHz, DMSO- $d_6$ )  $\delta$  ppm: 12.1 (br), 7.7 (d, 1 H), 7.6 (sl, 1 H), 7.27 (d, 1 H), 6.87 (d, 1 H), 6.76 (d, 1 H), 6.61 (dd, 1 H), 6.54 (d, 1 H), 6.45 (d, 1 H), 5.56 (q, 1 H), 4.85/4.52 (2d, 2 H), 4.85 (m, 2 H), 4.8 (t, 1 H), 3.92 (m, 2 H), 3.9/3.52 (2m, 2 H), 3.76 (m, 2 H), 3.57 (s, 3 H), 3.18/3.05 (2dd, 2 H), 2.85 (s, 3 H), 1.6 (d, 3 H)

**$^{13}C$ -NMR** (100 MHz, DMSO- $d_6$ )  $\delta$  ppm: 1561, 173.7, 154.8, 146.2, 145.4, 138.3, 135.4, 132.6, 131.5, 127.8, 125.2, 125.2, 124.6, 119.6, 118.1, 114.4, 113, 111, 109.7, 70.4, 68.8, 68.1, 55.6, 51.3, 48.5, 46, 40.6, 39.5, 19.6, 13.5

**$^{15}N$ -NMR** (50 MHz, DMSO- $d_6$ )  $\delta$  ppm: -152.9, -290.5

15

#### **Example 41b (2R,8R)**

**HRMS** calculated for  $C_{30}H_{32}N_4O_8S$ : 608.1941;  $[M+H]^+$  found: 609.2014 ( $\delta=0.1$  ppm)

**$^1H$ -NMR** (400 MHz, DMSO- $d_6$ )  $\delta$  ppm: 12.1 (br), 7.59 (d, 1 H), 7.46 (d, 1 H), 7.1 (d, 1 H), 7.08 (sl, 1 H), 6.89 (d, 1 H), 6.85 (d, 1 H), 6.73 (dd, 1 H), 5.71 (d, 1 H), 5.43 (q, 1 H), 4.85 (m, 1 H), 4.82 (m, 2 H), 4.17/4.12 (m, 2 H), 4.06/3.91 (dt+td, 2 H), 3.84/3.71 (2m, 2 H), 3.72 (s, 3 H), 3.62/3.52 (2m, 2 H), 2.97/2.84 (2dd, 2 H), 2.86 (s, 3 H), 1.35 (d, 3 H)

**$^{13}C$ -NMR** (100 MHz, DMSO- $d_6$ )  $\delta$  ppm: 173, 155.8, 155.4, 146.7, 145.2, 137.6, 136.1, 132.4, 128.7, 128.3, 127, 126.1, 125.5, 119.4, 118.5, 115, 113.3, 111.3, 108.9, 69.7, 68.7, 68.7, 55.9, 52.4, 48.6, 46.1, 41.3, 40.8, 17.7, 13.3

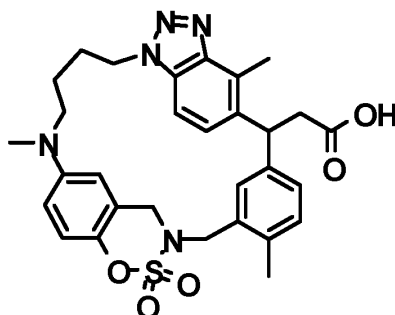
**$^{15}N$ -NMR** (50 MHz, DMSO- $d_6$ )  $\delta$  ppm: -3.1, -152.9, -290.5

25

**EXAMPLE 42** : [4,21,31-Trimethyl-27,27-dioxo-26-oxa-27 $\lambda^6$ -thia-1,14,15,16,21-pentaazahexacyclo[20.5.3.1<sup>3,7</sup>.1<sup>9,13</sup>.0<sup>12,16</sup>.0<sup>25,29</sup>]dotriaconta-3(32),4,6,9(31),10,12,14,22,24,29-decaen-8-yl]acetic acid

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**STEP C1 : Preparation of 6-bromo-2*H*-1,2λ<sup>6</sup>,3-benzoxathiazine-2,2-dione**

- 5 Using General Procedure 4 STEP 2 starting from 5-bromo-2-hydroxybenzaldehyde (1 eq.) as a reactant, the title compound (white solid, 38% yield) was obtained.

<sup>1</sup>H-NMR (400 MHz, DMSO-d<sub>6</sub>) δ ppm: 8.25 (d, 1 H), 8.15 (s, 1 H), 8.1 (dd, 1 H), 7.52 (d, 1 H)

10 **STEP C2 : Preparation of 6-bromo-3,4-dihydro-2*H*-1,2λ<sup>6</sup>,3-benzoxathiazine-2,2-dione**

Using General Procedure 4 STEP 3 starting from 6-bromo-2*H*-1,2λ<sup>6</sup>,3-benzoxathiazine-2,2-dione (1 eq.) as a reactant, the title compound ( white solid, 57% yield) was obtained.

- 15 <sup>1</sup>H-NMR (400 MHz, DMSO-d<sub>6</sub>) δ ppm: 8.6 (m, 1 H), 7.56 (d, 1 H), 7.52 (dd, 1 H), 7.05 (d, 1 H), 4.58 (s, 2 H)

**STEP 1: Preparation of ethyl 3-{3-[(6-bromo-2,2-dioxo-2*H*-1,2λ<sup>6</sup>,3-benzoxathiazin-3(4*H*)-yl)methyl]-4-methylphenyl}-3-(1-{4-[(4-methoxyphenyl)methoxy]butyl}-4-methyl-1*H*-benzotriazol-5-yl)propanoate**

20

Using General Procedure 7 starting from ethyl 3-[3-(hydroxymethyl)-4-methyl-phenyl]-3-[1-[4-[(4-methoxyphenyl)methoxy] butyl]-4-methyl-benzotriazol-5-yl]propanoate (1 eq.) and 6-bromo-3,4-dihydro-2*H*-1,2λ<sup>6</sup>,3-benzoxathiazine-2,2-dione (1.2 eq.) as reactants, the title compound (91% yield) was obtained.

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<sup>1</sup>H-NMR (400 MHz, DMSO-d<sub>6</sub>) δ ppm: 7.62 (dd, 1 H), 7.59/7.48 (2d, 2 H), 7.53 (d, 1 H), 7.24 (d, 1 H), 7.22-7.11 (m, 5 H), 6.86 (d, 2 H), 4.84 (t, 1 H), 4.65 (t, 2 H), 4.5 (m, 2 H), 4.31 (s, 2 H), 4.24 (m, 2 H), 3.93 (q, 2 H), 3.72 (s, 3 H), 3.37 (t, 2 H), 3.16 (d, 2 H), 2.76 (s, 3 H), 2.23 (s, 3 H), 1.92 (quint, 2 H), 1.48 (quint, 2 H), 0.99 (t, 3 H)

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**STEP 2 : Preparation of ethyl 3-[3-({6-[(*tert*-butoxycarbonyl)amino]-2,2-dioxo-2*H*-1,2λ<sup>6</sup>,3-benzoxathiazin-3(4*H*)-yl)methyl]-4-methylphenyl]-3-(1-{4-[(4-methoxyphenyl)methoxy]butyl}-4-methyl-1*H*-benzotriazol-5-yl)propanoate**

10 A 25 mL round bottom flask, equipped with drying tube was charged with ethyl 3-{3-[(6-bromo-2,2-dioxo-2*H*-1,2λ<sup>6</sup>,3-benzoxathiazin-3(4*H*)-yl)methyl]-4-methylphenyl}-3-(1-{4-[(4-methoxyphenyl)methoxy]butyl}-4-methyl-1*H*-benzotriazol-5-yl)propanoate (1 eq., 100 mg, 0.126 mmol), *tert*-butyl carbamate (1.2 eq., 17.8 mg, 0.152 mmol), sodium-*tert*-butoxide (1.5 eq., 18.2 mg, 0.189 mmol), tBuXPhos (0.2 eq., 10.7 mg, 0.0253 mmol) and Pd<sub>2</sub>(dba)<sub>3</sub> (0.1 eq., 11.6 mg, 0.0126 mmol) under argon flow. The mixture was suspended in toluene (1 mL) and stirred at RT overnight. The volatiles were evaporated under reduced pressure. The residue was purified by normal phase silica gel chromatography using hexane-EtOAc eluent to give the title compound (27 mg, 20% yield).

15 <sup>1</sup>H-NMR (400 MHz, DMSO-d<sub>6</sub>) δ ppm: 0.98 (t, J=7.09 Hz, 3 H) 1.15 - 1.28 (m, 13 H) 1.92 (quint, J=7.24 Hz, 2 H) 2.22 (s, 3 H) 2.75 (s, 3 H) 3.16 (d, J=7.46 Hz, 2 H) 3.36 (t, J=6.30 Hz, 3 H) 3.72 (s, 3 H) 3.86 - 3.97 (m, 2 H) 4.22 (s, 2 H) 4.30 (s, 2 H) 4.46 (s, 2 H) 4.64 (t, J=6.91 Hz, 2 H) 4.84 (t, J=8.07 Hz, 1 H) 6.12 (br. s., 2 H) 6.86 (d, J=8.68 Hz, 2 H) 6.92 (s, 1 H) 7.06 - 7.15 (m, 2 H) 7.18 (d, J=8.68 Hz, 2 H) 7.24 (s, 1 H) 7.36 (dd, J=9.05, 2.45 Hz, 1 H) 7.46 - 7.56 (m, 2 H) 7.59 (d, J=8.68 Hz, 1 H) 9.54 (s, 1 H)

25

**STEP 3 : Preparation of ethyl 3-[3-({6-[(*tert*-butoxycarbonyl)(methyl)amino]-2,2-dioxo-2*H*-1,2λ<sup>6</sup>,3-benzoxathiazin-3(4*H*)-yl)methyl]-4-methylphenyl]-3-(1-{4-[(4-methoxyphenyl)methoxy]butyl}-4-methyl-1*H*-benzotriazol-5-yl)propanoate**

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In a 100 mL round bottom flask, equipped with drying tube ethyl 3-[3-({6-[(*tert*-butoxycarbonyl)amino]-2,2-dioxo-2*H*-1,2λ<sup>6</sup>,3-benzoxathiazin-3(4*H*)-yl} methyl)-4-methylphenyl]-3-(1-{4-[(4-methoxyphenyl)methoxy]butyl}-4-methyl-1*H*-benzotriazol-5-yl)propanoate (1 eq., 260 mg, 0.289 mmol) was dissolved in DMF (2.4 mL). Sodium-hydride (60 % in mineral oil (1.5 eq., 17.3 mg, 0.433 mmol) was added portion-wise to the stirred mixture. After stirring for 5 min, iodomethane (1.5 eq., 61.5 mg, 0.027 mL) was added and the stirring was continued overnight at RT. The reaction mixture was poured into water (20 mL) and extracted with EtOAc (2x20 mL). The combined organic layers were washed with brine (20 mL) dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, the resulted filtrate was concentrated to dryness. The residue was purified by normal phase silica gel chromatography using heptane-EtOAc as an eluent to give the title compound (212 mg, 87% yield).

<sup>1</sup>H-NMR (400 MHz, DMSO-d<sub>6</sub>) δ ppm: 7.58 (d, 1 H), 7.48 (d, 1 H), 7.38-7.1 (m, 6 H), 7.19 (d, 2 H), 6.86 (d, 2 H), 4.82 (t, 1 H), 4.62 (t, 2 H), 4.49 (d, 2 H), 4.3 (s, 2 H), 4.22 (s, 2 H), 3.91 (q, 2 H), 3.71 (s, 3 H), 3.38 (t, 2 H), 3.2 (s, 3 H), 3.15 (m, 2 H), 2.5 (s, 3 H), 2.21 (s, 3 H), 1.9 (m, 2 H), 1.49 (m, 2 H), 1.4 (s, 9 H), 0.99 (t, 3 H)

**STEP 4 : Preparation of ethyl 3-[3-({6-[(*tert*-butoxycarbonyl)(methyl)amino]-2,2-dioxo-2*H*-1,2λ<sup>6</sup>,3-benzoxathiazin-3(4*H*)-yl} methyl)-4-methylphenyl]-3-[1-(4-hydroxybutyl)-4-methyl-1*H*-benzotriazol-5-yl]propanoate**

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Into a 25 mL round bottom flask equipped with drying tube ethyl 3-[3-({6-[(*tert*-butoxycarbonyl)(methyl)amino]-2,2-dioxo-2*H*-1,2λ<sup>6</sup>,3-benzoxathiazin-3(4*H*)-yl} methyl)-4-methylphenyl]-3-(1-{4-[(4-methoxyphenyl)methoxy]butyl}-4-methyl-1*H*-benzotriazol-5-yl)propanoate (1 eq., 0.262 g, 0.311 mmol), DCM (1.6 mL) and water (0.078 mL) were added. After addition of DDQ (1.5 eq., 106 mg, 0.467 mmol) the reaction mixture turned black, while additional stirring at RT for 3 h resulted a color change to red. The reaction mixture was diluted with DCM (20 mL), washed with sat. aq. NaHCO<sub>3</sub> solution (20 mL) and the aq. layer was extracted with DCM (20 mL). The combined organic layers were dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, the filtrate was concentrated. The residue was purified by normal phase silica gel chromatography using heptane-EtOAc as eluents to give the title compound (202 mg, 90%

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yield).

**<sup>1</sup>H-NMR** (400 MHz, DMSO-d<sub>6</sub>) δ ppm: 7.6 (d, 1 H), 7.45 (d, 1 H), 7.32 (dd, 1 H), 7.22 (d, 1 H), 7.17 (dd, 1 H), 7.15 (d, 1 H), 7.13 (d, 1 H), 4.83 (t, 1 H), 4.63 (t, 2 H), 4.5 (m, 2 H), 4.4 (t), 4.25 (s, 2 H), 4.23 (d, 1 H), 3.92 (q, 2 H), 3.38 (q, 2 H), 3.2 (s, 3 H), 3.18 (m, 2 H), 2.75 (s, 3 H), 2.21 (s, 3 H), 1.9 (m, 2 H), 1.4 (s, 9 H), 1.38 (m, 2 H), 1 (t, 3 H)

**STEP 5 : Preparation of ethyl 3-[1-(4-bromobutyl)-4-methyl-1*H*-benzotriazol-5-yl]-3-[3-({6-[(*tert*-butoxycarbonyl)(methyl)amino]-2,2-dioxo-2*H*-1,2λ<sup>6</sup>,3-benzoxathiazin-3(4*H*)-yl}methyl)-4-methylphenyl]propanoate**

10

Using General Procedure 9 starting from ethyl 3-[3-({6-[(*tert*-butoxycarbonyl)(methyl)amino]-2,2-dioxo-2*H*-1,2λ<sup>6</sup>,3-benzoxathiazin-3(4*H*)-yl}methyl)-4-methylphenyl]-3-[1-(4-hydroxybutyl)-4-methyl-1*H*-benzotriazol-5-yl]propanoate (1 eq.) as a reactant, the title compound (188 mg, 83% yield) was obtained.

**<sup>1</sup>H-NMR** (400 MHz, DMSO-d<sub>6</sub>) δ ppm: 7.6 (d, 1 H), 7.5 (d, 1 H), 7.33 (dd, 1 H), 7.3-7.1 (m, 5 H), 4.82 (t, 1 H), 4.68 (t, 2 H), 4.5 (m, 2 H), 4.22 (m, 2 H), 3.92 (q, 2 H), 3.52 (t, 2 H), 3.19 (s, 3 H), 3.18 (m, 2 H), 2.75 (s, 3 H), 2.2 (s, 3 H), 1.99 (m, 2 H), 1.78 (m, 2 H), 1.4 (s, 9 H), 1 (t, 3 H)

**STEP 6 : Preparation of ethyl 3-[1-(4-bromobutyl)-4-methyl-1*H*-benzotriazol-5-yl]-3-(4-methyl-3-{{6-(methylamino)-2,2-dioxo-2*H*-1,2λ<sup>6</sup>,3-benzoxathiazin-3(4*H*)-yl}methyl}phenyl)propanoate**

In a 100 mL round bottom flask equipped with drying tube ethyl 3-[1-(4-bromobutyl)-4-methyl-1*H*-benzotriazol-5-yl]-3-[3-({6-[(*tert*-butoxycarbonyl)(methyl)amino]-2,2-dioxo-2*H*-1,2λ<sup>6</sup>,3-benzoxathiazin-3(4*H*)-yl}methyl)-4-methylphenyl]propanoate (1 eq., 0.181 g, 0.231 mmol) was dissolved in DCM (3.6 mL). TFA (16 eq., 0.282 mL, 0.420 g, 3.7 mmol) was added dropwise, and the mixture was stirred at RT for 9 h. After completion of the reaction, the pH was set to 8-9 using sat. aq. Na<sub>2</sub>CO<sub>3</sub> solution. The layers were separated, the organic layer was washed with brine (10 mL) and the aq. layer was washed with DCM (10 mL). The combined organic layers



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were dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, and the filtrate was concentrated to dryness. The residue was purified by normal phase silica gel chromatography using heptane-EtOAc-EtOH (100:0:0 to 100/75/25) as eluents to give the title compound (0.117 g, 70% yield).

**<sup>1</sup>H-NMR** (400 MHz, DMSO-d<sub>6</sub>) δ ppm: 7.62 (d, 1 H), 7.51 (d, 1 H), 7.21 (sl, 1 H), 7.2 (d, 1 H), 7.14 (d, 1 H), 6.91 (d, 1 H), 6.57 (dd, 1 H), 6.29 (d, 1 H), 5.79 (q), 4.85 (t, 1 H), 4.69 (t, 2 H), 4.38/4.32 (m, 2 H), 4.22/4.15 (m, 2 H), 3.93 (q, 2 H), 3.53 (t, 2 H), 3.17 (m, 2 H), 2.76 (s, 3 H), 2.66 (d, 3 H), 2.22 (s, 3 H), 1.98 (m, 2 H), 1.77 (m, 2 H), 1 (t, 3 H)

**STEP 7 : Preparation of ethyl [4,21,31-trimethyl-27,27-dioxo-26-oxa-27λ<sup>6</sup>-thia-1,14,15,16,21-pentaazahexacyclo[20.5.3.1<sup>3,7</sup>.1<sup>9,13</sup>.0<sup>12,16</sup>.0<sup>25,29</sup>]dotriaconta-3(32),4,6,9(31),10,12,14,22,24,29-decaen-8-yl]acetate and ethyl [4,21,31-trimethyl-20,27,27-trioxo-26-oxa-27λ<sup>6</sup>-thia-1,14,15,16,21-pentaazahexacyclo[20.5.3.1<sup>3,7</sup>.1<sup>9,13</sup>.0<sup>12,16</sup>.0<sup>25,29</sup>]dotriaconta-3(32),4,6,9(31),10,12,14,22,24,29-decaen-8-yl]acetate**

Into a 100 mL round bottom flask equipped with a reflux condenser and a drying tube ethyl 3-[1-(4-bromobutyl)-4-methyl-1*H*-benzotriazol-5-yl]-3-(4-methyl-3-{{6-(methylamino)-2,2-dioxo-2*H*-1,2λ<sup>6</sup>,3-benzoxathiazin-3(4*H*)-yl]methyl}phenyl)propanoate (1 eq., 0.11 g, 0.161 mmol) and MeCN (48 mL) were added. Potassium iodide (0.1 eq., 2.667 mg, 0.0161 mmol) and Cs<sub>2</sub>CO<sub>3</sub> (2 eq., 6.2 g, 0.322 mmol) were added, and the mixture was stirred at 60°C for 24 h. After completion of the reaction, the mixture was concentrated under reduced pressure, the residue was diluted with EtOAc (40 mL) and washed with water (40 mL). The layers were separated, the organic layer was washed with brine, the combined aq. layers were washed with EtOAc (20 mL). The combined organic layer was dried over Na<sub>2</sub>SO<sub>4</sub>, then filtered, the filtrate was concentrated to dryness. The residue was purified by reversed-phase chromatography using water-MeCN-HCOOH (1000:25:1 to 25:1000:1) as eluent. The fractions containing of the 2 main products were individually combined and concentrated till water. The resulted aq. mixtures were freeze dried to give the title compounds:

**Ethyl [4,21,31-trimethyl-27,27-dioxo-26-oxa-27λ<sup>6</sup>-thia-1,14,15,16,21-pentaazahexacyclo**

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[20.5.3.1<sup>3,7</sup>.1<sup>9,13</sup>.0<sup>12,16</sup>.0<sup>25,29</sup>]dotriaconta-3(32),4,6,9(31),10,12,14,22,24,29-decaen-8-yl]acetate (28% yield)

<sup>1</sup>H-NMR (400 MHz, DMSO-d<sub>6</sub>) δ ppm: 7.66 (d, 1 H), 7.43 (dd, 1 H), 7.3 (d, 1 H), 7.27 (d, 1 H), 6.87 (d, 1 H), 6.64 (d, 1 H), 6.5 (dd, 1 H), 5.77 (d, 1 H), 4.82/4.72 (m, 2 H), 4.72 (m, 1 H),  
 5 4.24/3.94 (d, 2 H), 3.99/3.73 (d, 2 H), 3.94 (q, 2 H), 3.26/3.02 (dd, 2 H), 3.13/2.97 (m, 2 H),  
 2.83 (s, 3 H), 2.72 (s, 3 H), 2.32 (s, 3 H), 2.12/1.81 (m, 2 H), 1.47/1.04 (m, 2 H), 1.01 (t, 3 H)

**Ethyl** [4,21,31-trimethyl-20,27,27-trioxo-26-oxa-27λ<sup>6</sup>-thia-1,14,15,16,21-pentaazahexacyclo

[20.5.3.1<sup>3,7</sup>.1<sup>9,13</sup>.0<sup>12,16</sup>.0<sup>25,29</sup>]dotriaconta-3(32),4,6,9(31),10,12,14,22,24,29-decaen-8-yl]acetate (42% yield)

<sup>1</sup>H-NMR (400 MHz, DMSO-d<sub>6</sub>) δ ppm: 7.6 (d, 1 H), 7.5 (dd, 1 H), 7.33 (d, 1 H), 7.29 (m, 2 H), 7.08 (d, 1 H), 6.97 (sl, 1 H), 6.2 (sl, 1 H), 4.87/4.58 (m, 2 H), 4.87 (m, 1 H), 4.3/3.69 (m, 2 H), 4.2 (m, 2 H), 3.92 (q, 2 H), 3.22/3.1 (2dd, 2 H), 3.2 (s, 3 H), 2.4/2.03 (m, 2 H), 2.3 (s, 3 H),  
 15 2.2 (s, 3 H), 2.02/1.75 (m, 2 H), 1 (t, 3 H)

#### STEP 8 : Preparation of EXAMPLE 42

Using General Procedure 12 starting from ethyl [4,21,31-trimethyl-27,27-dioxo-26-oxa-27λ<sup>6</sup>-thia-1,14,15,16,21-pentaazahexacyclo[20.5.3.1<sup>3,7</sup>.1<sup>9,13</sup>.0<sup>12,16</sup>.0<sup>25,29</sup>]dotriaconta-3(32),4,6,9(31),10,12,14,22,24,29-decaen-8-yl]acetate (1 eq., 47 mg, 0.0779 mmol) as a  
 20 reactant, the title compound (25 mg, 54% yield) was obtained.

**HRMS** calculated for C<sub>30</sub>H<sub>33</sub>N<sub>5</sub>O<sub>5</sub>S: 575.2202; [M+H]<sup>+</sup> found: 576.2277 (δ=0.3 ppm)

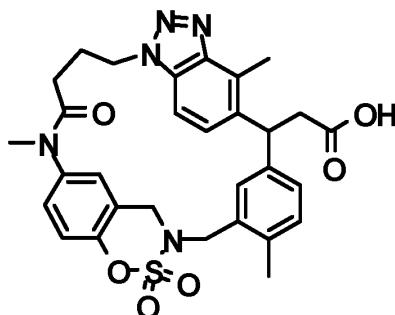
<sup>1</sup>H-NMR (400 MHz, DMSO-d<sub>6</sub>) δ ppm: 12.3 (m, 1 H), 7.64 (d, 1 H), 7.45 (dd, 1 H), 7.27 (d, 1 H), 7.26 (d, 1 H), 6.87 (d, 1 H), 6.63 (d, 1 H), 6.49 (dd, 1 H), 5.77 (d, 1 H), 4.82/4.72 (2m, 2 H),  
 25 4.78 (m, 1 H), 4.25/3.91 (2d, 2 H), 3.99/3.73 (2d, 2 H), 3.14/2.99 (2dd, 2 H), 3.1/2.97 (2m, 2 H),  
 2.83 (s, 3 H), 2.72 (s, 3 H), 2.32 (s, 3 H), 2.12/1.81 (2m, 2 H), 1.47/1.04 (2m, 2 H).

**EXAMPLE 43** : [4,21,31-Trimethyl-20,27,27-trioxo-26-oxa-27λ<sup>6</sup>-thia-1,14,15,16,21-

pentaazahexacyclo[20.5.3.1<sup>3,7</sup>.1<sup>9,13</sup>.0<sup>12,16</sup>.0<sup>25,29</sup>]dotriaconta-3(32),4,6,9(31),10,12,14,22,24,29-decaen-8-yl]acetic acid

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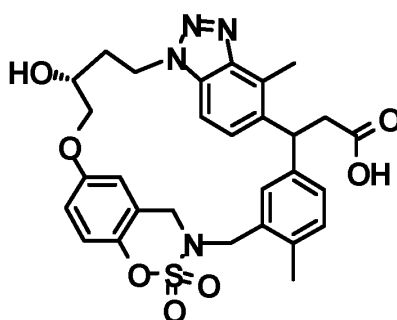


Using General Procedure 12 starting from ethyl [4,21,31-trimethyl-20,27,27-trioxo-26-oxa-27 $\lambda^6$ -thia-1,14,15,16,21-pentaazahexacyclo[20.5.3.1<sup>3,7</sup>.1<sup>9,13</sup>.0<sup>12,16</sup>.0<sup>25,29</sup>]dotriaconta-3(32),4,6,9(31),10,12,14,22,24,29-decaen-8-yl]acetate (1 eq., 71 mg, 0.1149 mmol) as a reactant, the title compound (35 mg, 50% yield) was obtained.

**HRMS** calculated for  $\text{C}_{30}\text{H}_{31}\text{N}_5\text{O}_6\text{S}$ : 589.1995;  $[\text{M}+\text{H}]^+$  found: 590.2074 ( $\delta=1.0$  ppm)

**<sup>1</sup>H-NMR** (400 MHz, DMSO-d<sub>6</sub>) δ ppm: 11.8 (m, 1 H), 7.6 (d, 1 H), 7.53 (dd, 1 H), 7.35 (d, 1 H), 7.29 (d, 1 H), 7.27 (dd, 1 H), 7.07 (d, 1 H), 6.94 (sl, 1 H), 6.2 (sl, 1 H), 4.87/4.58 (m, 2 H), 4.87 (m, 1 H), 4.27/3.69 (m, 2 H), 4.19 (m, 2 H), 3.21 (s, 3 H), 3.13/3 (2dd, 2 H), 2.51 (s, 3 H), 2.4/2.03 (m, 2 H), 2.31 (s, 3 H), 2.02/1.75 (m, 2 H)

**EXAMPLE 44** : [(19*R*)-19-hydroxy-4,31-dimethyl-27,27-dioxo-21,26-dioxa-27λ<sup>6</sup>-thia-1,14,15,16-tetraazahexacyclo[20.5.3.1<sup>3,7</sup>.1<sup>9,13</sup>.0<sup>12,16</sup>.0<sup>25,29</sup>]dotriaconta-3(32).4,6,9(31).10,12,14,22,24,29-decaen-8-yl]acetic acid



### STEP A1 : Preparation of 1-bromo-4-fluoro-2-methyl-3-nitrobenzene

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In a 3-necked round bottomed flask equipped with a thermostat 1-fluoro-3-methyl-2-nitrobenzene (1 eq., 50 g, 322.31 mmol) was dissolved in TFA (200 mL, 2.611 mol) and the reaction mixture was cooled to -5°C. Sulphuric acid (100 mL) was added dropwise, followed by addition of 1-bromopyrrolidine-2,5-dione (1 eq., 57.33 g, 322.1 mmol) in small portions. The reaction mixture was stirred at -5°C overnight, then at 0°C for 72 hours, and at 5°C for another night. The mixture was poured to a 1:1 mixture of ice/water, the precipitated solid was filtered out and washed with water. The obtained solid was dissolved in DCM and washed with sat. aq. NaHCO<sub>3</sub> solution and brine, dried over MgSO<sub>4</sub>, evaporated and dried on air at RT overnight to give 47.38 g (63% yield) of the title compound as an off-white solid.

<sup>1</sup>H-NMR (500 MHz, DMSO-d<sub>6</sub>) δ ppm: 7.98 (dd, 1 H), 7.49 (td, 1 H), 2.37 (s, 3 H)

#### STEP A2 : Preparation of (2R)-4-(4-bromo-3-methyl-2-nitroanilino)butane-1,2-diol

The solution of 1-bromo-4-fluoro-2-methyl-3-nitrobenzene (1 eq., 4 g, 17 mmol), (2R)-4-aminobutane-1,2-diol hydrochloride (1.5 eq., 4.6 mL, 3.6 g, 25 mmol) and DIPEA (2 eq., 6 mL, 4.452 g, 34.45 mmol) in N,N-dimethylacetamide (38 eq., 60 mL, 56.2 g, 645.3 mmol) was stirred at 100 °C overnight. After addition of another 0.74 g (5.22 mmol) of (2R)-4-aminobutane-1,2-diol hydrochloride and 1 ml of DIPEA, the reaction mixture was stirred for additional 6h at 100°C. The reaction mixture was poured on ice, extracted with EtOAc, and the aq. layer was back-extracted with EtOAc. The combined organic layers were washed with brine, dried over Na<sub>2</sub>SO<sub>4</sub> and concentrated under reduced pressure. The crude product was purified by normal phase silica gel chromatography using heptane-EtOAc (100:0 to 60:40) as eluents. Collection and evaporation of the fractions containing of the product resulted in the title compound (4.13 g, 76% yield) as an orange solid.

<sup>1</sup>H-NMR (500 MHz, DMSO-d<sub>6</sub>) δ ppm: 7.54 (d, 1 H), 6.74 (d, 1 H), 6.29 (t, 1 H), 4.72 (d, 1 H), 4.55 (t, 1 H), 3.5 (m, 1 H), 3.23/3.131 (dd+m, 2 H), 3.22 (q, 2 H), 2.25 (s, 3 H), 1.75/1.45 (m+m, 2 H)

#### STEP A3 : Preparation of (2R)-4-(4-bromo-3-methyl-2-nitro-anilino)-1-[tert-butyl(dimethyl)silyl]oxy-butan-2-ol

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(2R)-4-(4-Bromo-3-methyl-2-nitroanilino)butane-1,2-diol (1 eq., 3 g, 9.40 mmol) was dissolved in dry DMF (18 mL) and DIPEA (4.2 mL, 24 mmol) was added. The mixture was cooled to 0°C prior to the dropwise addition of a solution of *tert*-butyl(chloro)dimethylsilane (1.5 g, 10 mmol) in DMF (5.5 mL). The temperature was allowed to warm to RT and the mixture was stirred at this temperature overnight. The reaction mixture was poured on sat. NH<sub>4</sub>Cl solution and extracted with DCM. The organic phase was washed with brine, dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated. The residual DMF was removed by evaporation in high vacuo. The crude product was purified by normal phase silica gel chromatography using heptane-EtOAc (100:0 to 75:25) as eluents to give the title compound (3.898 g, 96% yield) as an orange solid.

<sup>1</sup>H-NMR (500 MHz, DMSO-d<sub>6</sub>) δ ppm: 7.53 (d, 1 H), 6.73 (d, 1 H), 6.27 (t, 1 H), 4.78 (d, 1 H), 3.52 (m, 1 H), 3.51/3.36 (m+m, 2 H), 3.23 (q, 2 H), 2.25 (s, 3 H), 1.78/1.44 (m+m, 2 H), 0.84 (s, 9 H), 0.02 (s, 6 H)

**STEP A4 : Preparation of 4-bromo-*N*-[(3R)-4-{*tert*-butyl(dimethyl)silyl]oxy}-3-{*tert*-butyl(diphenyl)silyl]oxy}butyl]-3-methyl-2-nitroaniline**

(2R)-4-(4-Bromo-3-methyl-2-nitro-anilino)-1-[*tert*-butyl(dimethyl)silyl]oxy-butan-2-ol (1 eq., 3.898 g, 8.994 mmol) was dissolved in dry DMF (45 mL), and imidazole (3 eq., 1.83 g, 26.9 mmol) was added followed by addition of *N,N*-dimethylpyridin-4-amine (0.113 g, 0.925 mmol). The reaction mixture was cooled to 0°C and *tert*-butyl(chloro)diphenylsilane (2 eq., 4.96 g, 18.0 mmol) was added dropwise. The temperature was raised to 50°C and the mixture was stirred at this temperature overnight. The reaction mixture was poured on sat. NH<sub>4</sub>Cl solution and extracted with DCM. The organic phase was washed with sat. NaHCO<sub>3</sub> solution, then with brine, dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and evaporated. The residual DMF was removed by evaporation in high vacuo. The crude product was purified by normal phase silica gel chromatography using DCM eluent to give the title compound (5.92 g, 98% yield) as an orange oil.

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<sup>1</sup>H-NMR (500 MHz, DMSO-d<sub>6</sub>) δ ppm: 7.65-7.35 (m, 10 H), 7.44 (d, 1 H), 6.52 (d, 1 H), 6.06 (t, 1 H), 3.82 (m, 1 H), 3.46/3.44 (dd+dd, 2 H), 3.17/3.13 (m+m, 2 H), 2.24 (s, 3 H), 1.8/1.7 (m+m, 2 H), 0.99 (s, 3 H), 0.76 (s, 3 H), -0.12/-0.16 (s, 6 H)

5     **STEP A5 : Preparation of 4-bromo-N<sup>1</sup>-[(3R)-4-{[*tert*-butyl(dimethyl)silyl]oxy}-3-{[*tert*-butyl(diphenyl)silyl]oxy}butyl]-3-methylbenzene-1,2-diamine**

4-Bromo-N-[(3R)-4-{[*tert*-butyl(dimethyl)silyl]oxy}-3-{[*tert*-butyl(diphenyl)silyl]oxy}butyl]-3-methyl-2-nitroaniline (1 eq., 6.0 g, 8.9 mmol) was dissolved in a mixture of dioxane (30 mL) and MeOH (5 mL). Raney nickel catalyst (0.38 g, 4.4 mmol), washed with dioxane was added and the mixture was hydrogenated in a stainless steel autoclave under 10 bar pressure at RT for 3 h. After completion of the reaction the mixture was filtered through a pad of Celite, washed with DCM and the mother liquor was evaporated to dryness to give the title compound (5.63 g, 98% yield) as a brownish thick oil, which was used in a next step without purification.

15     <sup>1</sup>H-NMR (500 MHz, DMSO-d<sub>6</sub>) δ ppm: 7.69-7.37 (m, 10 H), 6.65 (d, 1 H), 6.1 (d, 1 H), 4.55 (s, 2 H), 4.52 (t, 1 H), 3.87 (m, 1 H), 3.48/3.46 (dd+dd, 2 H), 3.04/2.97 (m+m, 2 H), 2.15 (s, 3 H), 1.87/1.79 (m+m, 2 H), 1 (s, 9 H), 0.77 (s, 3 H), -0.11 (s, 3 H), -0.14 (s, 3 H)

20     **STEP A6 : Preparation of 5-bromo-1-[(3R)-4-{[*tert*-butyl(dimethyl)silyl]oxy}-3-{[*tert*-butyl(diphenyl)silyl]oxy}butyl]-4-methyl-1H-benzotriazole**

4-Bromo-N<sup>1</sup>-[(3R)-4-{[*tert*-butyl(dimethyl)silyl]oxy}-3-{[*tert*-butyl(diphenyl)silyl]oxy}butyl]-3-methylbenzene-1,2-diamine (1 eq., 5.0 g, 7.8 mmol) was dissolved in abs. THF (40 mL) and the mixture was cooled to 0°C. TFA (10 mg, 0.0612 mmol) was added to the mixture followed by the dropwise addition of 3-methylbutyl nitrite (1.66 eq., 1.8 mL, 13 mmol) at 0°C. The reaction mixture was stirred for 3h, while the temperature was allowed to raise to RT. The mixture was diluted with THF and evaporated to Celite. The crude product was purified by normal phase silica gel chromatography using heptane-EtOAc (100:0 to 98:2) as eluents, resulted in a title compound (2.46 g, 48% yield) as a dark orange thick oil.

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<sup>1</sup>H-NMR (500 MHz, DMSO-d<sub>6</sub>) δ ppm: 7.64 (d, 1 H), 7.6-7.31 (m, 10 H), 7.43 (d, 1 H), 3.75 (m, 1 H), 3.74 (t, 2 H), 3.47/3.43 (dd+dd, 2 H), 2.7 (s, 3 H), 2.19/2.04 (m+m, 2 H), 0.98 (s, 9 H), 0.7 (s, 9 H), -0.17/-0.23 (s+s, 6 H)

5 **STEP A7 : Preparation of ethyl (2E)-3-{1-[(3R)-4-{[tert-butyl(dimethyl)silyl]oxy}-3-{[tert-butyl(diphenyl)silyl]oxy}butyl]-4-methyl-1H-benzotriazol-5-yl}prop-2-enoate**

5-Bromo-1-[(3R)-4-{[tert-butyl(dimethyl)silyl]oxy}-3-{[tert-butyl(diphenyl)silyl]oxy}butyl]-  
 10 4-methyl-1H-benzotriazole (1 eq., 2.455 g, 3.76 mmol) was dissolved in abs. DMF (10 mL) in a microwave tube. Ethyl prop-2-enoate (2 eq., 0.805 mL, 7.40 mmol) was added followed by an addition of DIPEA (1.95 mL, 11.375 mmol). The reaction mixture was flushed with N<sub>2</sub> prior to the addition of (acetato-κO)({2-[bis(2-methylphenyl)phosphanyl]phenyl}methyl)palladium (0.1 eq., 0.359 g, 0.382 mmol). The mixture was flushed again with N<sub>2</sub>, the tube was sealed and  
 15 placed into the microwave reactor for 2 h at 150°C. The mixture was filtered through a pad of celite, the filter cake was washed with DCM and the mother liquor was evaporated to celite. The crude product was purified by normal phase silica gel chromatography using heptane-EtOAc (100:0 to 80:20) as eluents resulting the title compound (2.19 g, 88% yield) as a yellow thick oil.

20 <sup>1</sup>H-NMR (500 MHz, DMSO-d<sub>6</sub>) δ ppm: 8.02 (d, 1 H), 7.93 (d, 1 H), 7.62-7.31 (m, 10 H), 7.46 (d, 1 H), 6.66 (d, 1 H), 4.74 (t, 2 H), 4.22 (q, 2 H), 3.78 (m, 1 H), 3.49/3.45 (dd+dd, 2 H), 2.8 (s, 3 H), 2.19/2.05 (m+m, 2 H), 1.28 (t, 3 H), 0.99 (s, 9 H), 0.71 (s, 9 H), -0.16/-0.21 (s+s, 6 H)

25 **STEP 1: Preparation of ethyl 3-{1-[(3R)-4-{[tert-butyl(dimethyl)silyl]oxy}-3-{[tert-butyl(diphenyl)silyl]oxy}butyl]-4-methyl-1H-benzotriazol-5-yl}-3-[3-(hydroxymethyl)-4-methylphenyl]propanoate**

Ethyl (2E)-3-{1-[(3R)-4-{[tert-butyl(dimethyl)silyl]oxy}-3-{[tert-butyl(diphenyl)silyl]oxy}butyl]-4-methyl-1H-benzotriazol-5-yl}prop-2-enoate (1 eq., 1.43 g, 2.13 mmol) was dissolved  
 30

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in dioxane (10 mL) and [2-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]methanol (1.55 eq., 0.81 g, 3.3 mmol) was added followed by addition of TEA (1.4 eq., 0.42 mL, 3.0 mmol) and water (2 mL). The reaction mixture was flushed with N<sub>2</sub> prior to the addition of chloro(1,5-cyclooctadiene)rhodium(I) dimer catalyst (0.051 g, 0.10 mmol). After stirring at 80°C overnight the mixture was filtered through a pad of Celite, the filter cake was washed with DCM, the mother liquor was evaporated and the residue was taken up in heptane. The mixture was purified by normal phase silica gel chromatography using heptane-EtOAc (100:0 to 60:40) as eluents, resulting the title compound (0.99 g, 59% yield) as a colourless thick oil.

**<sup>1</sup>H-NMR** (500 MHz, DMSO-d<sub>6</sub>) δ ppm: 7.62-7.28 (m, 10 H), 7.43 (d, 1 H), 7.34 (d, 1 H), 7.29/7.27 (d/d, 1 H), 7.1/7.08 (dd/dd, 1 H), 7.03/7.01 (d/d, 1 H), 5/4.99 (t/t, 1 H), 4.83 (t, 1 H), 4.67 (t, 2 H), 4.41/4.4 (d/d, 2 H), 3.92 (m, 2 H), 3.76 (m, 1 H), 3.44 (m, 2 H), 3.13 (m, 2 H), 2.75 (s, 3 H), 2.15 (s, 3 H), 2.15/2.02 (m+m, 2 H), 1.01/1 (t/t, 3 H), 0.97 (s, 9 H), 0.7/0.68 (s/s, 9 H), -0.18/-0.19/-0.23/-0.26 (s/s/s/s, 6 H)

**STEP 2 : Preparation of ethyl 3-(3-{[6-(benzyloxy)-2,2-dioxo-2H-1,2λ<sup>6</sup>,3-benzoxathiazin-3(4H)-yl]methyl}-4-methylphenyl)-3-{1-[(3R)-4-{[tert-butyl(dimethyl)silyl]oxy}-3-{[tert-butyl(diphenyl)silyl]oxy}butyl]-4-methyl-1H-benzotriazol-5-yl}propanoate**

Ethyl 3-{1-[(3R)-4-{[tert-butyl(dimethyl)silyl]oxy}-3-{[tert-butyl(diphenyl)silyl]oxy}butyl]-4-methyl-1H-benzotriazol-5-yl}-3-[3-(hydroxymethyl)-4-methylphenyl]propanoate (1 eq., 0.882 g, 1.11 mmol), 6-(benzyloxy)-3,4-dihydro-2H-1,2λ<sup>6</sup>,3-benzoxathiazine-2,2-dione (0.696 g, 2.39 mmol) and PPh<sub>3</sub> (0.57 g, 2.2 mmol) were suspended in dry THF (20 mL) and DIAD (0.27 g, 1.3 mmol) was added in one portion. The reaction mixture was stirred at RT for 24h. The mixture was diluted with DCM, evaporated to Celite and purified by normal phase silica gel chromatography using heptane-EtOAc (100:0 to 80:20) as eluents, resulting the title compound (0.707 g, 60% yield) as a white solid.

**<sup>1</sup>H-NMR** (500 MHz, DMSO-d<sub>6</sub>) δ ppm: 7.62-7.28 (m, 18 H), 7.45 (d, 1 H), 7.34 (d, 1 H), 7.13 (d, 1 H), 7.06 (dd, 1 H), 6.96/6.94 (d/d, 1 H), 5.09 (s, 2 H), 4.86 (t, 1 H), 4.66 (m, 2 H), 4.43 (m,



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2 H), 4.2 (s, 2 H), 3.92 (m, 2 H), 3.76 (m, 1 H), 3.42 (m, 2 H), 3.18 (m, 2 H), 2.76 (s, 3 H), 2.22/2.21 (s/s, 3 H), 2.15/2 (m+m, 2 H), 0.99/0.98 (t/t, 3 H), 0.95 (s, 9 H), 0.69/0.66 (s/s, 9 H), -0.2/-0.22/-0.25/-0.3 (s/s/s/s, 6 H)

5 **STEP 3: Preparation of ethyl 3-{1-[(3R)-4-{[*tert*-butyl(dimethyl)silyl]oxy}-3-{[*tert*-butyl(diphenyl)silyl]oxy}butyl]-4-methyl-1*H*-benzotriazol-5-yl}-3-{3-[(6-hydroxy-2,2-dioxo-2*H*-1,2λ<sup>6</sup>,3-benzoxathiazin-3(4*H*)-yl)methyl]-4-methylphenyl}propanoate**

10 Ethyl 3-(3-{[6-(benzyloxy)-2,2-dioxo-2*H*-1,2λ<sup>6</sup>,3-benzoxathiazin-3(4*H*)-yl]methyl}-4-methylphenyl)-3-{1-[(3R)-4-{[*tert*-butyl(dimethyl)silyl]oxy}-3-{[*tert*-butyl(diphenyl)silyl]oxy}butyl]-4-methyl-1*H*-benzotriazol-5-yl}propanoate (1 eq., 0.577 g, 0.541 mmol) was dissolved in a mixture of dioxane (2 mL) and MeOH (6 mL), and Pd/C (0.05 g, 0.05 mmol) was added to the mixture, which was hydrogenated in a stainless steel autoclave under 2 bars at RT  
15 overnight. After completion of the reaction the mixture was filtered through a pad of Celite, the filter cake was washed with DCM, the mother liquor was concentrated, the residue was dried in high vacuo at RT to yield the title compound (0.485 g, 92% yield) as a white foamy material. The product was used in a next step without purification.

<sup>1</sup>H-NMR (500 MHz, DMSO-d<sub>6</sub>) δ ppm: 9.7 (s, 1 H), 7.61-7.08 (m, 13 H), 7.47 (d, 1 H), 7.36  
20 (d, 1 H), 6.99 (d, 1 H), 6.79 (dd, 1 H), 6.61 (d, 1 H), 4.85 (t, 1 H), 4.68 (m, 2 H), 4.41/4.36 (d+d, 2 H), 4.21/4.16 (d+d, 2 H), 3.93 (m, 2 H), 3.74 (m, 1 H), 3.43 (m, 2 H), 3.17 (m, 2 H), 2.75 (s, 3 H), 2.22/2.21 (s/s, 3 H), 2.16/2.02 (m+m, 2 H), 1.01/1 (t/t, 3 H), 0.96 (s, 9 H), 0.69/0.66 (s/s, 9 H), -0.2/-0.21/-0.25/-0.29 (s/s/s/s, 6 H)

25 **STEP 4: Preparation of ethyl 3-{1-[(3R)-3-{[*tert*-butyl(diphenyl)silyl]oxy}-4-hydroxybutyl]-4-methyl-1*H*-benzotriazol-5-yl}-3-{3-[(6-hydroxy-2,2-dioxo-2*H*-1,2λ<sup>6</sup>,3-benzoxathiazin-3(4*H*)-yl)methyl]-4-methylphenyl}propanoate**

Ethyl 3-{1-[(3R)-4-{[*tert*-butyl(dimethyl)silyl]oxy}-3-{[*tert*-butyl(diphenyl)silyl]oxy}butyl]-  
30 4-methyl-1*H*-benzotriazol-5-yl}-3-{3-[(6-hydroxy-2,2-dioxo-2*H*-1,2λ<sup>6</sup>,3-benzoxathiazin-

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3(4*H*)-yl)methyl]-4-methylphenyl}propanoate (1 eq., 0.47 g, 0.48 mmol) was dissolved in EtOH (30 mL). 2M aq. hydrochloric acid (0.5 mL, 1 mmol) was added and the mixture was stirred at RT for 3h. After completion of the reaction the mixture was cooled to 0°C and neutralized with 0.15 ml of TEA. The mixture was diluted with DCM, evaporated to Celite and purified by normal phase silica gel chromatography using DCM-MeOH (100:0 to 80:20) as eluents, resulting the title compound (0.335 g, 81% yield) as a white solid.

<sup>1</sup>H-NMR (500 MHz, DMSO-d<sub>6</sub>) δ ppm: 9.7 (s, 1 H), 7.61-7.09 (m, 13 H), 7.47 (d, 1 H), 7.36 (d, 1 H), 6.99 (d, 1 H), 6.79 (dd, 1 H), 6.62/6.61 (d, 1 H), 4.84 (t, 1 H), 4.74 (t, 1 H), 4.66 (t, 2 H), 4.41/4.36 (d+d, 2 H), 4.22/4.17 (d+d, 2 H), 3.93 (m, 2 H), 3.74 (m, 1 H), 3.38 (m, 2 H), 3.17 (m, 2 H), 2.76/2.75 (s/s, 3 H), 2.22/2.21 (s/s, 3 H), 2.15/2.02 (m+m, 2 H), 1.01/1 (t/t, 3 H), 0.96 (s, 9 H)

**STEP 5 : Preparation of ethyl 3-{1-[(3*R*)-3-{[*tert*-butyl(diphenyl)silyl]oxy}-4-chlorobutyl]-4-methyl-1*H*-benzotriazol-5-yl}-3-{3-[(6-hydroxy-2,2-dioxo-2*H*-1,2λ<sup>6</sup>,3-benzoxathiazin-3(4*H*)-yl)methyl]-4-methylphenyl}propanoate**

Using General Procedure 10 starting from ethyl 3-{1-[(3*R*)-3-{[*tert*-butyl(diphenyl)silyl]oxy}-4-hydroxybutyl]-4-methyl-1*H*-benzotriazol-5-yl}-3-{3-[(6-hydroxy-2,2-dioxo-2*H*-1,2λ<sup>6</sup>,3-benzoxathiazin-3(4*H*)-yl)methyl]-4-methylphenyl}propanoate (1 eq.) as a reactant, the title compound (colorless oil, 33% yield) was obtained.

<sup>1</sup>H-NMR (500 MHz, DMSO-d<sub>6</sub>) δ ppm: 9.72 (brs, 1 H), 7.54-7.11 (m, 15 H), 6.99 (d, 1 H), 6.79 (dd, 1 H), 6.6 (d, 1 H), 4.85 (t, 1 H), 4.63 (t, 2 H), 4.4/4.36 (d+d, 2 H), 4.21/4.17 (d+d, 2 H), 3.93 (q, 2 H), 3.93 (dd, 1 H), 3.67 (d, 2 H), 3.18 (m, 2 H), 2.76/2.75 (s, 3 H), 2.22 (s, 3 H), 2.2/2.11 (m+m, 2 H), 1.01/0.99 (t/t, 3 H), 0.96/0.95 (s/s, 9 H)

**STEP 6 : Preparation of ethyl [(19*R*)-19-{[*tert*-butyl(diphenyl)silyl]oxy}-4,31-dimethyl-27,27-dioxo-21,26-dioxa-27λ<sup>6</sup>-thia-1,14,15,16-tetraazahexacyclo[20.5.3.1<sup>3,7</sup>.1<sup>9,13</sup>.0<sup>12,16</sup>.0<sup>25,29</sup>]dotriaconta-3(32),4,6,9(31),10,12,14,22,24,29-decaen-8-yl]acetate**

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Using General Procedure 11 starting from ethyl 3-{1-[(3*R*)-3-{[*tert*-butyl(diphenyl)silyl]oxy}-4-chlorobutyl]-4-methyl-1*H*-benzotriazol-5-yl}-3-{3-[(6-hydroxy-2,2-dioxo-2*H*-1,2λ<sup>6</sup>,3-benzoxathiazin-3(4*H*)-yl)methyl]-4-methylphenyl}propanoate (1 eq.) as a reactant, the title compound (39% yield) was obtained.

5 <sup>1</sup>H-NMR (500 MHz, DMSO-d<sub>6</sub>) δ ppm: 7.75-7.25 (m, 12 H), 7.51/7.48 (d/d, 1 H), 7.31/7.29 (d/d, 1 H), 6.92/6.85 (d/d, 1 H), 6.55/6.52 (d/d, 1 H), 6.43/6.3 (dd/dd, 1 H), 5.36/5.28 (d/d, 1 H), 4.92/4.64 (m+m, 2 H), 4.8 (m, 1 H), 4.32/4.16 (m/m, 1 H), 4.29/3.72 (d+d, 2 H), 4.01/3.61 (d+d, 2 H), 3.94/3.92 (q/q, 2 H), 3.41/3.14 (dd+m, 2 H), 3.12 (m, 2 H), 2.59/2.52 (s/s, 3 H), 2.5/2.36 (m+m, 2 H), 2.33/2.32 (s/s, 3 H), 1.07 (s, 9 H), 1.03 (t, 3 H)

10

**STEP 7 : Preparation of ethyl [(19*R*)-19-hydroxy-4,31-dimethyl-27,27-dioxo-21,26-dioxa-27λ<sup>6</sup>-thia-1,14,15,16-tetraazahexacyclo[20.5.3.1<sup>3,7</sup>.1<sup>9,13</sup>.0<sup>12,16</sup>.0<sup>25,29</sup>]dotriaconta-3(32),4,6,9(31),10,12,14,22,24,29-decaen-8-yl]acetate**

15

Ethyl [(19*R*)-19-{[*tert*-butyl(diphenyl)silyl]oxy}-4,31-dimethyl-27,27-dioxo-21,26-dioxa-27λ<sup>6</sup>-thia-1,14,15,16-tetraazahexacyclo[20.5.3.1<sup>3,7</sup>.1<sup>9,13</sup>.0<sup>12,16</sup>.0<sup>25,29</sup>]dotriaconta-3(32),4,6,9(31),10,12,14,22,24,29-decaen-8-yl]acetate (1 eq., 30 mg, 0.03550 mmol) was dissolved in THF (2 mL) and 1 M tetrabutylammonium-fluoride in THF (1.5 eq., 0.053 mL, 20 0.053 mmol) was added. The reaction mixture was stirred at RT for 24h. The mixture was diluted with DMF, and purified via preparative reversed-phase C18 column chromatography by direct injection, resulting in 15 mg (70% yield) of the title compound as a white solid foam.

<sup>1</sup>H-NMR (500 MHz, DMSO-d<sub>6</sub>) δ ppm: 7.66/7.65 (d, 1 H), 7.49/7.4 (d, 1 H), 7.48 (dd, 1 H), 7.3/7.27 (d, 1 H), 7.02/7 (d, 1 H), 6.84/6.83 (dd, 1 H), 6.57/6.46 (d, 1 H), 6.03/5.74 (d, 1 H), 25 5.33/5.28 (brs, 1 H), 4.94-4.7 (m, 2 H), 4.78 (m, 1 H), 4.24-3.75 (d+d, 4 H), 3.93 (q, 2 H), 3.85/3.69 (m, 1 H), 3.57/3.34 (m, 2 H), 3.24-2.99 (dd+dd, 2 H), 2.61/2.6 (s, 3 H), 2.41/2.26 (m+m, 2 H), 2.33/2.32 (s, 3 H), 1.01 (t, 3 H)

**STEP 8 : Preparation of EXAMPLE 44**

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Using General Procedure 12 starting from ethyl [(19*R*)-19-hydroxy-4,31-dimethyl-27,27-dioxo-21,26-dioxa-27 $\lambda^6$ -thia-1,14,15,16-tetraazahexacyclo[20.5.3.1<sup>3,7</sup>.1<sup>9,13</sup>.0<sup>12,16</sup>.0<sup>25,29</sup>] dotriaconta-3(32),4,6,9(31),10,12,14,22,24,29-decaen-8-yl]acetate (1 eq.) as reactant, the title compound (white solid, 92% yield) was obtained.

5

**HRMS** calculated for C<sub>29</sub>H<sub>30</sub>N<sub>4</sub>O<sub>7</sub>S: 578.1835; [M+H]<sup>+</sup> found: 579.1906 ( $\delta$  = -0.3 ppm)

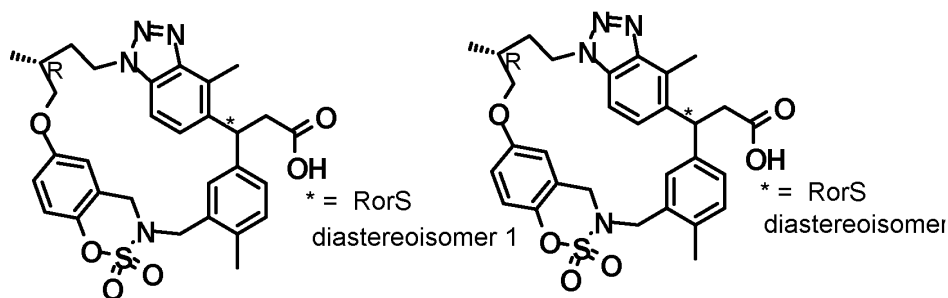
**<sup>1</sup>H-NMR** (500 MHz, DMSO-d<sub>6</sub>)  $\delta$  ppm: 7.6/7.58 (d/d, 1 H), 7.54/7.51 (brd/brd., 1 H), 7.41/7.35 (d/d, 1 H), 7.24/7.21 (d/d, 1 H), 7/6.99 (d/d, 1 H), 6.83/6.82 (dd/dd, 1 H), 6.37/6.31 (d/d, 1 H), 5.94/5.7 (brd/d, 1 H), 5.46/5.29 (brd/d, 1 H), 4.9-4.68 (m, 2 H), 4.8 (m, 1 H), 4.07-3.87 (m, 2 H), 3.99/3.87 (d+d, 2 H), 3.86/3.72 (br/br., 1 H), 3.55-3.24 (m, 2 H), 2.59-2.34 (m, 2 H), 2.56/2.55 (s/s, 3 H), 2.4/2.3 (m+m, 2 H), 2.31/2.3 (s/s, 3 H)

10

**<sup>13</sup>C-NMR** (125 MHz, DMSO-d<sub>6</sub>)  $\delta$  ppm: 173.4, 155.9, 144.5, 131.3, 131.1/131, 129.1, 128.2, 119.7/119.5, 117.6/117.3, 116.9, 111.3/11.1, 107.4/107.3, 73/72.4, 65.9/65.8, 52.2/51.8, 48.8/48.6, 46.9, 43.9/43.6, 43.5/43, 32.9, 18.5/18.4, 13.5

15

**EXAMPLE 45** : [(19*R*)-4,19,31-Trimethyl-27,27-dioxo-21,26-dioxa-27 $\lambda^6$ -thia-1,14,15,16-tetraazahexacyclo[20.5.3.1<sup>3,7</sup>.1<sup>9,13</sup>.0<sup>12,16</sup>.0<sup>25,29</sup>]dotriaconta-3(32),4,6,9(31),10,12,14,22,24,29-decaen-8-yl]acetic acid



20

**STEP A1 : Preparation of ethyl (2*E*)-3-(4-fluoro-2-methyl-3-nitrophenyl)prop-2-enoate**

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The mixture of 1-bromo-4-fluoro-2-methyl-3-nitrobenzene (1 eq., 50 g, 213.66 mmol), ethyl (2*E*)-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)prop-2-enoate (1.15 eq., 55.55 g, 245.71 mmol), sodium carbonate (2.5 eq., 56.61 g, 534.14 mmol) dissolved in THF (250 mL) and water (250 mL) was purged with N<sub>2</sub> prior to the addition of A<sup>tr</sup>phos.PdCl<sub>2</sub> (0.02 eq., 1.9 g, 4.2731 mmol). The reaction mixture was heated at reflux for 2h under N<sub>2</sub> atmosphere. 500 ml EtOAc and 250 ml water were added. The layers were separated, the aq. layer was extracted with 2x20 ml EtOAc, the combined organic layers were dried over MgSO<sub>4</sub>, filtered and evaporated under reduced pressure. The residue was purified by filtration through 250 g silica gel in a glass filter with 4 L heptane-EtOAc (90:10). The fractions containing of the product were collected and evaporated under reduced pressure. The residue was taken up in 30 ml heptane and crystallised by sonication. The precipitated solid was filtered and dried in vacuo at 40°C overnight to yield 48.48 g (89.6% yield) of the title compound as a white solid.

<sup>1</sup>H-NMR (500 MHz, DMSO-d<sub>6</sub>) δ ppm: 8.06 (dd, 1 H), 7.8 (d, 1 H), 7.52 (t, 1 H), 6.64 (d, 1 H), 4.21 (q, 2 H), 2.36 (s, 3 H), 1.27 (t, 3 H)

**STEP 1 : Preparation of 6-(benzyloxy)-3-[(5-bromo-2-methylphenyl)methyl]-3,4-dihydro-2*H*-1,2λ<sup>6</sup>,3-benzoxathiazine-2,2-dione**

Using General Procedure 7 starting from (5-bromo-2-methylphenyl)methanol (1 eq.) and 6-(benzyloxy)-3,4-dihydro-2*H*-1,2λ<sup>6</sup>,3-benzoxathiazine-2,2-dione (0.83 eq.) as reactants, the title compound (65% yield) was obtained as a white solid.

<sup>1</sup>H-NMR (500 MHz, DMSO-d<sub>6</sub>) δ ppm: 7.47 (d, 1 H), 7.46 (dd, 1 H), 7.44 (d, 2 H), 7.4 (t, 2 H), 7.34 (t, 1 H), 7.21 (d, 1 H), 7.13 (d, 1 H), 7.06 (d, 1 H), 7.05 (dd, 1 H), 5.08 (s, 2 H), 4.57 (s, 2 H), 4.29 (s, 2 H), 2.24 (s, 3 H)

**STEP 2 : Preparation of 6-(benzyloxy)-3-{[2-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]methyl}-3,4-dihydro-2*H*-1,2λ<sup>6</sup>,3-benzoxathiazine-2,2-dione**

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Using General Procedure 3 starting from 6-(benzyloxy)-3-[(5-bromo-2-methylphenyl)methyl]-3,4-dihydro-2*H*-1,2λ<sup>6</sup>,3-benzoxathiazine-2,2-dione (1 eq.) as a reactant, the title compound (56% yield) was obtained as a white solid.

<sup>1</sup>H-NMR (500 MHz, DMSO-d<sub>6</sub>) δ ppm: 7.58 (d, 1 H), 7.54 (s, 1 H), 7.47-7.31 (m, 5 H), 7.27 (d, 1 H), 7.15 (d, 1 H), 7.05 (dd, 1 H), 7.04 (d, 1 H), 5.07 (s, 2 H), 4.5 (s, 2 H), 4.29 (s, 2 H), 2.29 (s, 3 H), 1.29 (s, 12 H)

**STEP 3 : Preparation of ethyl 3-(3-{[6-(benzyloxy)-2,2-dioxo-2*H*-1,2λ<sup>6</sup>,3-benzoxathiazin-3(4*H*)-yl]methyl}-4-methylphenyl)-3-(4-fluoro-2-methyl-3-nitrophenyl)propanoate**

Using General Procedure 6 starting from ethyl (2*E*)-3-(4-fluoro-2-methyl-3-nitrophenyl)prop-2-enoate (1 eq.) and 6-(benzyloxy)-3-[[2-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]methyl]-3,4-dihydro-2*H*-1,2λ<sup>6</sup>,3-benzoxathiazine-2,2-dione (1.15 eq.) as reactants, the title compound (white solid, 51% yield) was obtained.

<sup>1</sup>H-NMR (500 MHz, DMSO-d<sub>6</sub>) δ ppm: 7.69 (dd, 1 H), 7.47-7.31 (m, 5 H), 7.42 (m, 1 H), 7.2 (d, 1 H), 7.17 (d, 1 H), 7.15 (dd, 1 H), 7.14 (d, 1 H), 7.07 (dd, 1 H), 6.96 (d, 1 H), 5.09 (s, 2 H), 4.67 (t, 1 H), 4.44 (s, 2 H), 4.22 (s, 2 H), 3.97 (q, 2 H), 3.2/3.1 (dd+dd, 2 H), 2.27 (s, 3 H), 2.23 (s, 3 H), 1.04 (t, 3 H)

**STEP 4 : Preparation of ethyl 3-(3-{[6-(benzyloxy)-2,2-dioxo-2*H*-1,2λ<sup>6</sup>,3-benzoxathiazin-3(4*H*)-yl]methyl}-4-methylphenyl)-3-(4-{[(3*R*)-4-hydroxy-3-methylbutyl]amino}-2-methyl-3-nitrophenyl)propanoate**

To a solution of ethyl 3-(3-{[6-(benzyloxy)-2,2-dioxo-2*H*-1,2λ<sup>6</sup>,3-benzoxathiazin-3(4*H*)-yl]methyl}-4-methylphenyl)-3-(4-fluoro-2-methyl-3-nitrophenyl)propanoate (1 eq., 2.57 g, 3.96 mmol) and DIPEA (3 eq., 1.54 g, 11.9 mmol, 2.07 mL) in DMSO (13 mL) (2*R*)-4-amino-2-methylbutan-1-ol (1.3 eq., 0.531 g, 5.15 mmol) was added. The reaction mixture was stirred at 80 °C for 18 h. The reaction mixture was poured into brine (150 ml), and the aq. layer was extracted with EtOAc (150 ml). The organic layer was dried over MgSO<sub>4</sub>, filtered and

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evaporated. The residue was purified by normal phase silica gel chromatography using heptane-EtOAc eluents to give the title compound (1.90 g, 62% yield)

**<sup>1</sup>H-NMR** (500 MHz, DMSO-d<sub>6</sub>) δ ppm: 7.5-7.3 (m, 5 H), 7.33 (d, 1 H), 7.15 (d, 1 H), 7.15 (d, 1 H), 7.14 (d, 1 H), 7.1 (dd, 1 H), 7.07 (dd, 1 H), 6.98 (d, 1 H), 6.7 (d, 1 H), 5.68 (t, 1 H), 5.1 (s, 2 H), 4.53 (t, 1 H), 4.46 (t, 1 H), 4.44 (s, 2 H), 4.23/4.2 (d+d, 2 H), 3.96 (q, 2 H), 3.22/3.19 (m+m, 2 H), 3.11/3.07 (m+m, 2 H), 3.05/3.002 (dd+dd, 2 H), 2.22 (s, 3 H), 2.13 (s, 3 H), 1.58/1.24 (m+m, 2 H), 1.52 (m, 1 H), 1.04 (t, 3 H), 0.83 (d, 3 H)

**STEP 5 : Preparation of ethyl 3-(3-amino-4-[(3*R*)-4-hydroxy-3-methylbutyl]amino}-2-methylphenyl)-3-(3-{[6-(benzyloxy)-2,2-dioxo-2*H*-1,2λ<sup>6</sup>,3-benzoxathiazin-3(4*H*)-yl]methyl}-4-methylphenyl)propanoate**

To a solution of ethyl 3-(3-{[6-(benzyloxy)-2,2-dioxo-2*H*-1,2λ<sup>6</sup>,3-benzoxathiazin-3(4*H*)-yl]methyl}-4-methylphenyl)-3-(4-[(3*R*)-4-hydroxy-3-methylbutyl]amino}-2-methyl-3-nitrophenyl)propanoate (1 eq., 1.58 g, 2.16 mmol) in 1,2-dichloroethane (15 mL) and IPA (15 mL) Raney nickel catalyst (1.5 g) was added. To the suspension hydrazine hydrate (5 eq., 5.40 g, 10.8 mmol, 5.24 mL) was added dropwise over 3 min. The reaction mixture was stirred at RT for 90 min. The reaction mixture was filtered through a pad of Celite, and the Celite was washed with DCM (3x20 ml). The filtrate was evaporated to give the title compound (1.4 g, 92% yield).

**<sup>1</sup>H-NMR** (500 MHz, DMSO-d<sub>6</sub>) δ ppm: 7.49-7.31 (m, 5 H), 7.14 (d, 1 H), 7.1 (d, 1 H), 7.07 (dd, 1 H), 7.06 (d, 1 H), 7.02 (dd, 1 H), 6.98 (d, 1 H), 6.48 (d, 1 H), 6.31 (d, 1 H), 5.11 (s, 2 H), 4.52 (t, 1 H), 4.44 (t, 1 H), 4.41 (s, 2 H), 4.21/4.14 (d+d, 2 H), 3.95 (m, 2 H), 3.27/3.22 (m+m, 2 H), 3/2.94 (m+m, 2 H), 2.9 (m, 2 H), 2.21 (s, 3 H), 1.96 (s, 3 H), 1.66/1.32 (m+m, 2 H), 1.64 (m, 1 H), 1.05 (t, 3 H), 0.86 (d, 3 H)

25

**STEP 6 : Preparation of ethyl 3-(3-{[6-(benzyloxy)-2,2-dioxo-2*H*-1,2λ<sup>6</sup>,3-benzoxathiazin-3(4*H*)-yl]methyl}-4-methylphenyl)-3-{1-[(3*R*)-4-hydroxy-3-methylbutyl]-4-methyl-3*a*,7*a*-dihydro-1*H*-benzotriazol-5-yl}propanoate**

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To a solution of ethyl 3-(3-amino-4-[(3*R*)-4-hydroxy-3-methylbutyl]amino)-2-methylphenyl)-3-(3-{[6-(benzyloxy)-2,2-dioxo-2*H*-1,2λ<sup>6</sup>,3-benzoxathiazin-3(4*H*)-yl]methyl}-4-methylphenyl)propanoate (1 eq., 1.10 g, 1.6 mmol) in DCM (25 mL) 3-methylbutyl nitrite (3 eq., 550 mg, 4.7 mmol, 0.63 mL) was added in one portion. The reaction mixture was stirred at RT for 1 day. The reaction mixture was diluted with DCM (100 ml) and washed with brine (100 ml). The organic layer was dried over MgSO<sub>4</sub>, filtered and evaporated. The residue was purified by normal phase silica gel chromatography using heptane-EtOAc eluents to give the title compound (560 mg, 50% yield).

<sup>1</sup>H-NMR (500 MHz, DMSO-d<sub>6</sub>) δ ppm: 7.51 (d, 1 H), 7.49 (d, 1 H), 7.48-7.32 (m, 5 H), 7.24 (m, 1 H), 7.19 (dd, 1 H), 7.14 (d, 1 H), 7.14 (d, 1 H), 7.07 (dd, 1 H), 6.97 (d, 1 H), 5.1 (s, 2 H), 4.84 (t, 1 H), 4.65 (m, 2 H), 4.48 (t, 1 H), 4.44 (s, 2 H), 4.22 (s, 2 H), 3.92 (q, 2 H), 3.22 (m, 2 H), 3.18 (m, 2 H), 2.76 (s, 3 H), 2.21 (s, 3 H), 1.98/1.59 (m+m, 2 H), 1.39 (m, 1 H), 0.98 (t, 3 H), 0.86 (d, 3 H)

**STEP 7: Preparation of ethyl 3-{3-[(6-hydroxy-2,2-dioxo-2*H*-1,2λ<sup>6</sup>,3-benzoxathiazin-3(4*H*)-yl)methyl]-4-methylphenyl}-3-{1-[(3*R*)-4-hydroxy-3-methylbutyl]-4-methyl-3a,7a-dihydro-1*H*-benzotriazol-5-yl}propanoate**

Using General Procedure 8 starting from ethyl 3-(3-{[6-(benzyloxy)-2,2-dioxo-2*H*-1,2λ<sup>6</sup>,3-benzoxathiazin-3(4*H*)-yl]methyl}-4-methylphenyl)-3-{1-[(3*R*)-4-hydroxy-3-methylbutyl]-4-methyl-3a,7a-dihydro-1*H*-benzotriazol-5-yl}propanoate (1 eq., 560 mg, 0.7856 mmol) as a reactant, the title compound (460 mg, 94% yield) was obtained.

<sup>1</sup>H-NMR (500 MHz, DMSO-d<sub>6</sub>) δ ppm: 9.7 (s, 1 H), 7.61 (d, 1 H), 7.51 (d, 1 H), 7.22 (d, 1 H), 7.2 (dd, 1 H), 7.13 (d, 1 H), 6.99 (d, 1 H), 6.79 (dd, 1 H), 6.61 (d, 1 H), 4.84 (t, 1 H), 4.68 (t, 2 H), 4.5 (brs, 1 H), 4.38 (s, 2 H), 4.21/4.17 (d+d, 2 H), 3.93 (q, 2 H), 3.24 (m, 2 H), 3.19/3.15 (dd+dd, 2 H), 2.75 (s, 3 H), 2.22 (s, 3 H), 2/1.61 (m+m, 2 H), 1.42 (m, 1 H), 1 (t, 3 H), 0.88 (d, 3 H)



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**STEP 8 : Preparation of ethyl 3-{1-[(3*R*)-4-chloro-3-methylbutyl]-4-methyl-3a,7a-dihydro-1*H*-benzotriazol-5-yl}-3-{3-[(6-hydroxy-2,2-dioxo-2*H*-1,2λ<sup>6</sup>,3-benzoxathiazin-3(4*H*)-yl)methyl]-4-methylphenyl}propanoate**

5 Using General Procedure 10 starting from ethyl 3-{3-[(6-hydroxy-2,2-dioxo-2*H*-1,2λ<sup>6</sup>,3-benzoxathiazin-3(4*H*)-yl)methyl]-4-methylphenyl}-3-{1-[(3*R*)-4-hydroxy-3-methylbutyl]-4-methyl-3a,7a-dihydro-1*H*-benzotriazol-5-yl}propanoate (1 eq., 460 mg, 0.7387 mmol) as a reactant, the title compound (470 mg, 99% yield) was obtained.

<sup>1</sup>H-NMR (500 MHz, DMSO-d<sub>6</sub>) δ ppm: 9.71 (s, 1 H), 7.63 (d, 1 H), 7.52 (d, 1 H), 7.22 (d, 1 H), 7.2 (dd, 1 H), 7.13 (d, 1 H), 6.99 (d, 1 H), 6.79 (dd, 1 H), 6.6 (d, 1 H), 4.84 (t, 1 H), 4.71 (t, 2 H), 4.38 (s, 2 H), 4.21/4.17 (d+d, 2 H), 3.93 (q, 2 H), 3.63/3.6 (dd+dd, 2 H), 3.17 (d, 2 H), 2.76 (s, 3 H), 2.22 (s, 3 H), 2.04/1.77 (m+m, 2 H), 1.74 (m, 1 H), 1.01 (d, 3 H), 0.99 (t, 3 H)

**STEP 9 : Preparation of ethyl [(19*R*)-4,19,31-trimethyl-27,27-dioxo-21,26-dioxa-27λ<sup>6</sup>-thia-15 1,14,15,16-tetraazahexacyclo[20.5.3.1<sup>3,7</sup>.1<sup>9,13</sup>.0<sup>12,16</sup>.0<sup>25,29</sup>]dotriaconta-3(32),4,6,9(31),10,12,14,22,24,29-decaen-8-yl]acetate**

Using General Procedure 11 starting from ethyl 3-{1-[(3*R*)-4-chloro-3-methylbutyl]-4-methyl-3a,7a-dihydro-1*H*-benzotriazol-5-yl}-3-{3-[(6-hydroxy-2,2-dioxo-2*H*-1,2λ<sup>6</sup>,3-benzoxathiazin-3(4*H*)-yl)methyl]-4-methylphenyl}propanoate (1 eq., 470 mg, 0.7330 mmol) as a reactant, the title compound (110 mg, 25% yield) was obtained.

<sup>1</sup>H-NMR (500 MHz, DMSO-d<sub>6</sub>, mixture of diastereomers) δ ppm: 7.68/7.65 (d/d, 1 H), 7.5/7.35 (d/d, 1 H), 7.48 (dd, 1 H), 7.3/7.28 (d/d, 1 H), 7/6.98 (d/d, 1 H), 6.81 (dd, 1 H), 6.56/6.53 (d/d, 1 H), 5.83/5.77 (d/d, 1 H), 4.83/4.79/4.75 (m+m/m, 2 H), 4.8/4.79 (t/t, 1 H), 4.18/4.09/4/3.87 (d/d+d/d, 2 H), 4.03/3.94/3.89/3.75 (d/d+d/d, 2 H), 3.92 (m, 2 H), 3.67/3.42/3.36 (m/dd+dd, 2 H), 3.22/3.14/3.06/3.02 (dd+dd/dd+dd, 2 H), 2.64/2.59 (s/s, 3 H), 2.33/2.11/2.02/1.95 (m+m/m+m, 2 H), 2.32 (s, 3 H), 2.11/1.6 (m/m, 1 H), 1.1/1.04 (d/d, 3 H), 1.01/1 (t/t, 3 H)

**STEP 10 : Preparation of EXAMPLE 45**

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Using General Procedure 12 starting from ethyl [(19*R*)-4,19,31-trimethyl-27,27-dioxo-21,26-dioxa-27 $\lambda^6$ -thia-1,14,15,16-tetraazahexacyclo[20.5.3.1<sup>3,7</sup>.1<sup>9,13</sup>.0<sup>12,16</sup>.0<sup>25,29</sup>]dotriacont-3(32),4,6,9(31),10,12,14,22,24,29-decaen-8-yl]acetate (1 eq., 110 mg, 0.1819 mmol) as a reactant, the title compound (90 mg, 86% yield) was obtained.

- 5 The diastereoisomers were obtained by chromatographic separation on chiral column.

**Example 45a (19*R*, dia1)**

<sup>1</sup>H-NMR (500 MHz, DMSO-d<sub>6</sub>)  $\delta$  ppm: 12.22 (br., 1 H), 7.64 (d, 1 H), 7.49 (d, 1 H), 7.49 (d, 1 H), 7.28 (d, 1 H), 7 (d, 1 H), 6.81 (dd, 1 H), 6.54 (d, 1 H), 5.75 (d, 1 H), 4.82/4.74 (dm+m, 2 H), 4.75 (t, 1 H), 4.17/3.87 (d+d, 2 H), 4.04/3.75 (d+d, 2 H), 3.35 (m, 2 H), 3.03/2.95 (dd+dd, 2 H), 2.58 (s, 3 H), 2.32 (s, 3 H), 2.12/2.03 (m+m, 2 H), 2.12 (m, 1 H), 1.1 (d, 3 H)

10 <sup>13</sup>C-NMR (125 MHz, DMSO-d<sub>6</sub>)  $\delta$  ppm: 173.2, 131.2, 131.2, 128.8, 127.4, 119.5, 117.4, 111.1, 107.7, 72.4, 51.8, 48.7, 46.2, 42, 41, 33.8, 32.3, 18.4, 17.1, 13.4

15 **Example 45b (19*R*, dia2)**

HRMS calculated for C<sub>30</sub>H<sub>32</sub>N<sub>4</sub>O<sub>6</sub>S: 576.2042; [M+H]<sup>+</sup> found: 577.212 ( $\delta$  = 0.8 ppm)

<sup>1</sup>H-NMR (500 MHz, DMSO-d<sub>6</sub>)  $\delta$  ppm: 12.2 (br., 1 H), 7.68 (d, 1 H), 7.49 (dd, 1 H), 7.34 (d, 1 H), 7.3 (d, 1 H), 6.99 (d, 1 H), 6.81 (dd, 1 H), 6.51 (d, 1 H), 5.83 (d, 1 H), 4.79 (m, 2 H), 4.78 (m, 1 H), 4.1/4 (d+d, 2 H), 3.95/3.89 (d+d, 2 H), 3.67/3.41 (dd+dd, 2 H), 3.11/2.91 (dd+dd, 2 H), 2.63 (s, 3 H), 2.34/1.96 (m+m, 2 H), 2.32 (s, 3 H), 1.61 (m, 1 H), 1.04 (d, 3 H)

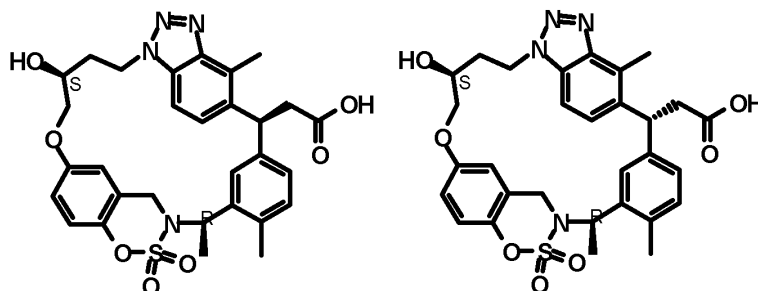
20 <sup>13</sup>C-NMR (125 MHz, DMSO-d<sub>6</sub>)  $\delta$  ppm: 173.3, 131.6, 131.3, 128.1, 127.4, 119.5, 116.8, 112, 108.2, 72.8, 51.8, 48.6, 45.9, 41.3, 40.7, 31.5, 29.9, 18.4, 16.6, 13.4

**EXAMPLE 46 : [(2*R*,8*RS*,19*S*)-19-Hydroxy-2,4,31-trimethyl-27,27-dioxo-21,26-dioxa-**

25 **27 $\lambda^6$ -thia-1,14,15,16-tetraazahexacyclo[20.5.3.1<sup>3,7</sup>.1<sup>9,13</sup>.0<sup>12,16</sup>.0<sup>25,29</sup>]dotriacont-3(32),4,6,9(31),10,12,14,22,24,29-decaen-8-yl]acetic acid and [(2*R*,8*RS*,19*S*)-19-hydroxy-2,4,31-trimethyl-27,27-dioxo-21,26-dioxa-27 $\lambda^6$ -thia-1,14,15,16-**

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**tetraazahexacyclo[20.5.3.1<sup>3,7</sup>.1<sup>9,13</sup>.0<sup>12,16</sup>.0<sup>25,29</sup>]dotriaconta-  
3(32),4,6,9(31),10,12,14,22,24,29-decaen-8-yl]acetic acid**



**5 STEP A1 : Preparation of (2*S*)-4-(4-bromo-3-methyl-2-nitroanilino)butane-1,2-diol**

A mixture of 1-bromo-4-fluoro-2-methyl-3-nitrobenzene (1 eq., 6 g, 26 mmol), (2*S*)-4-aminobutane-1,2-diol hydrochloride (1.5 eq., 6.9 mL, 5.40 g, 38 mmol) and DIPEA (2 eq., 9 mL, 6.68 g, 51.67 mmol) was stirred in *N,N*-dimethylacetamide (120 mL) at 100 °C over the weekend. The reaction mixture was poured on crushed ice, extracted with EtOAc, and the aq. layer was washed with EtOAc. The combined organic layers were washed with brine, dried over Na<sub>2</sub>SO<sub>4</sub>, concentrated under reduced pressure. The residue was purified by normal phase silica gel chromatography using DCM-MeOH eluents to give the title compound (7.47 g, 91% yield). <sup>1</sup>H-NMR (500 MHz, DMSO-*d*<sub>6</sub>) δ ppm: 7.54 (d, 1 H), 6.74 (d, 1 H), 6.29 (t, 1 H), 4.72 (d, 1 H), 4.55 (t, 1 H), 3.5 (m, 1 H), 3.23/3.131 (dd+m, 2 H), 3.22 (q, 2 H), 2.25 (s, 3 H), 1.75/1.45 (m+m, 2 H)

**STEP A2 : Preparation of (2*S*)-4-(4-bromo-3-methyl-2-nitroanilino)-1-{{*tert*-butyl(dimethyl)silyl}oxy}butan-2-ol**

20

(2*S*)-4-(4-Bromo-3-methyl-2-nitroanilino)butane-1,2-diol (1 eq., 7.29 g, 22.8 mmol) was dissolved in dry DMF (44 mL) and DIPEA (2.51 eq., 10 mL, 7.42 g, 57.41 mmol, 2.51 equiv) was added. The reaction mixture was cooled to 0°C prior to the dropwise addition of *tert*-butyl(chloro)dimethylsilane (1.06 eq., 4.2 mL, 3.65 g, 24.2 mmol), dissolved in dry DMF (13

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mL). The temperature was allowed to raise to RT, and the mixture was stirred at this temperature overnight. The reaction mixture was poured on sat.  $\text{NH}_4\text{Cl}$  solution, extracted with EtOAc, and the aq. layer was washed with EtOAc. The combined organic layers were washed with brine, dried over  $\text{Na}_2\text{SO}_4$ , concentrated. The residue was purified by normal phase silica gel chromatography using heptane-EtOAc eluents to give the title compound (8.30 g, 84% yield).

$^1\text{H-NMR}$  (500 MHz,  $\text{DMSO-d}_6$ )  $\delta$  ppm: 7.53 (d, 1 H), 6.73 (d, 1 H), 6.27 (t, 1 H), 4.78 (d, 1 H), 3.52 (m, 1 H), 3.51/3.36 (m+m, 2 H), 3.23 (q, 2 H), 2.25 (s, 3 H), 1.78/1.44 (m+m, 2 H), 0.84 (s, 9 H), 0.02 (s, 6 H)

10 **STEP A3 : Preparation of 4-bromo-*N*-[(3*S*)-4-{*tert*-butyl(dimethyl)silyl]oxy}-3-{*tert*-butyl(diphenyl)silyl]oxy}butyl]-3-methyl-2-nitroaniline**

(2*S*)-4-(4-Bromo-3-methyl-2-nitroanilino)-1-{*tert*-butyl(dimethyl)silyl]oxy}butan-2-ol (1 eq., 8.24 g, 19.0 mmol) was dissolved in dry DMF (95 mL) and imidazole (3 eq., 3.87 g, 56.8 mmol) was added followed by the addition of *N,N*-dimethylpyridin-4-amine (0.1 eq., 0.238 g, 1.95 mmol). The reaction mixture was cooled to 0°C prior to the dropwise addition of *tert*-butylchloro-diphenyl-silane (2 eq., 10.5 g, 38.2 mmol). The temperature was allowed to raise to RT and the mixture was stirred at this temperature overnight. The reaction mixture was poured on cooled sat.  $\text{NH}_4\text{Cl}$  solution, extracted with DCM. The combined organic layers were washed with brine, dried over  $\text{Na}_2\text{SO}_4$ , concentrated under reduced pressure. The residue was purified by normal phase silica gel chromatography using heptane-EtOAc as eluents to give the title compound (13.37 g, quant.).

15  $^1\text{H-NMR}$  (500 MHz,  $\text{DMSO-d}_6$ )  $\delta$  ppm: 7.65-7.35 (m, 10 H), 7.44 (d, 1 H), 6.52 (d, 1 H), 6.06 (t, 1 H), 3.82 (m, 1 H), 3.46/3.44 (dd+dd, 2 H), 3.17/3.13 (m+m, 2 H), 2.24 (s, 3 H), 1.8/1.7 (m+m, 2 H), 0.99 (s, 3 H), 0.76 (s, 3 H), -0.12/-0.16 (s, 6 H)

25 **STEP A4 : Preparation of 4-bromo-*N*<sup>1</sup>-[(3*S*)-4-{*tert*-butyl(dimethyl)silyl]oxy}-3-{*tert*-butyl(diphenyl)silyl]oxy}butyl]-3-methylbenzene-1,2-diamine**

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4-Bromo-*N*-[(3*S*)-4-{[*tert*-butyl(dimethyl)silyl]oxy}-3-{[*tert*-butyl(diphenyl)silyl]oxy}butyl]-3-methyl-2-nitroaniline (1 eq., 13.0 g, 19.35mmol) was dissolved in dioxane (10 mL) and MeOH (50 mL). Raney nickel catalyst (0.5 eq., 0.8 g, 9.00 mmol) - washed with dioxane - was added to the mixture, which was hydrogenated in a stainless steel autoclave under 10 bar pressure at RT for 3 h. After completion of the reaction the mixture was filtered through a Celite pad, the Celite was washed with DCM, the mother liquor was concentrated. The residue was purified by normal phase silica gel chromatography using heptane-EtOAc eluents to give the title compound (10.90 g, 88% yield).

<sup>1</sup>H-NMR (500 MHz, DMSO-d<sub>6</sub>) δ ppm: 7.69-7.37 (m, 10 H), 6.65 (d, 1 H), 6.1 (d, 1 H), 4.55 (s, 2 H), 4.52 (t, 1 H), 3.87 (m, 1 H), 3.48/3.46 (dd+dd, 2 H), 3.04/2.97 (m+m, 2 H), 2.15 (s, 3 H), 1.87/1.79 (m+m, 2 H), 1 (s, 9 H), 0.77 (s, 3 H), -0.11 (s, 3 H), -0.14 (s, 3 H)

**STEP A5 : Preparation of 5-bromo-1-[(3*S*)-4-{[*tert*-butyl(dimethyl)silyl]oxy}-3-{[*tert*-butyl(diphenyl)silyl]oxy}butyl]-4-methyl-1*H*-benzotriazole**

4-Bromo-*N*<sup>1</sup>-[(3*S*)-4-{[*tert*-butyl(dimethyl)silyl]oxy}-3-{[*tert*-butyl(diphenyl)silyl]oxy}butyl]-3-methylbenzene-1,2-diamine (1 eq., 8.50 g, 13 mmol) was dissolved in abs. THF (40 mL) and the mixture was cooled to 0°C. 2,2,2-trichloroacetic acid (0.01 eq., 17.4 mg, 0.106 mmol) was added to the mixture followed by the dropwise addition of 3-methylbutyl nitrite (1.8 eq., 3.13 mL, 2.73 g, 13 mmol). The reaction mixture was stirred for 3h, while the temperature was allowed to warm to RT. The mixture was diluted with THF and evaporated to celite. The crude product was purified by normal phase silica gel chromatography using heptane-EtOAc eluents to give the title compound (4.67 g, 54% yield).

<sup>1</sup>H-NMR (500 MHz, DMSO-d<sub>6</sub>) δ ppm: 7.64 (d, 1 H), 7.6-7.31 (m, 10 H), 7.43 (d, 1 H), 3.75 (m, 1 H), 3.74 (t, 2 H), 3.47/3.43 (dd+dd, 2 H), 2.7 (s, 3 H), 2.19/2.04 (m+m, 2 H), 0.98 (s, 9 H), 0.7 (s, 9 H), -0.17/-0.23 (s+s, 6 H)

**STEP A6 : Preparation of ethyl (2*E*)-3-{1-[(3*S*)-4-{[*tert*-butyl(dimethyl)silyl]oxy}-3-{[*tert*-butyl(diphenyl)silyl]oxy}butyl]-4-methyl-1*H*-benzotriazol-5-yl}prop-2-enoate**

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5-Bromo-1-[(3*S*)-4-{[*tert*-butyl(dimethyl)silyl]oxy}-3-{[*tert*-butyl(diphenyl)silyl]oxy}butyl]-4-methyl-1*H*-benzotriazole (1 eq., 5.09 g, 7.80 mmol) was dissolved in abs. DMF (10 mL). Ethyl prop-2-enoate (2 eq., 1.70 mL 1.56 g, 15.6 mmol) and DIPEA (3 eq., 4.07 mL, 3.02 g, 23.4 mmol) were added, and the reaction mixture was flushed with N<sub>2</sub>. Acetoxy-[[2-(bis-*o*-tolylphosphanyl)phenyl]methyl]palladium (0.1 eq., 731 mg, 0.780 mmol) catalyst was added and the mixture was heated at 150 °C in a microwave reactor for 7 h. The mixture was filtered through a pad of Celite and the filtrate was purified by reversed-phase chromatography to give the title compound (2.58 g, 49% yield).

10 <sup>1</sup>H-NMR (500 MHz, DMSO-d<sub>6</sub>) δ ppm: 8.02 (d, 1 H), 7.93 (d, 1 H), 7.62-7.31 (m, 10 H), 7.46 (d, 1 H), 6.66 (d, 1 H), 4.74 (t, 2 H), 4.22 (q, 2 H), 3.78 (m, 1 H), 3.49/3.45 (dd+dd, 2 H), 2.8 (s, 3 H), 2.19/2.05 (m+m, 2 H), 1.28 (t, 3 H), 0.99 (s, 9 H), 0.71 (s, 9 H), -0.16/-0.21 (s+s, 6 H)

15 **STEP 1 : Preparation of 6-(benzyloxy)-3-[(1*R*)-1-(5-bromo-2-methylphenyl)ethyl]-3,4-dihydro-2*H*-1,2λ<sup>6</sup>,3-benzoxathiazine-2,2-dione**

Using General Procedure 7 starting from (1*R*)-1-(5-bromo-2-methylphenyl)ethan-1-ol (1.4 eq., 30.08 g, 139.8 mmol) and 6-(benzyloxy)-3,4-dihydro-2*H*-1,2λ<sup>6</sup>,3-benzoxathiazine-2,2-dione (1 eq., 29.10 g, 99.9 mmol) as reactants, the title compound (41.6 g, 85% yield) was obtained as a white solid.

20 <sup>1</sup>H-NMR (500 MHz, DMSO-d<sub>6</sub>) δ ppm: 7.6 (d, 1 H), 7.47-7.31 (m, 5 H), 7.44 (dd, 1 H), 7.2 (d, 1 H), 7.03 (d, 1 H), 7.03 (d, 1 H), 6.97 (dd, 1 H), 5.27 (q, 1 H), 5.09/5.06 (d+d, 2 H), 4.5 (s, 2 H), 2.33 (s, 3 H), 1.42 (d, 3 H)

25 **STEP 2 : Preparation of 6-(benzyloxy)-3-{(1*R*)-1-[2-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]ethyl}-3,4-dihydro-2*H*-1,2λ<sup>6</sup>,3-benzoxathiazine-2,2-dione**

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Using General Procedure 3 starting from 6-(benzyloxy)-3-[(1*R*)-1-(5-bromo-2-methylphenyl)ethyl]-3,4-dihydro-2*H*-1,2λ<sup>6</sup>,3-benzoxathiazine-2,2-dione (1 eq., 60 g, 122.9 mmol) as a reactant, the title compound (60.7 g, 92% yield) was obtained.

<sup>1</sup>H-NMR (500 MHz, DMSO-d<sub>6</sub>) δ ppm: 7.62 (d, 1 H), 7.58 (dd, 1 H), 7.43 (d, 2 H), 7.39 (t, 2 H), 7.33 (t, 1 H), 7.27 (d, 1 H), 7.04 (d, 1 H), 7.02 (d, 1 H), 6.98 (dd, 1 H), 5.3 (q, 1 H), 5.07/5.03 (d+d, 2 H), 4.4 (s, 2 H), 2.39 (s, 3 H), 1.44 (d, 3 H), 1.3 (s, 6 H), 1.29 (s, 6 H)

**STEP 3 : Preparation of ethyl 3-(3-{(1*R*)-1-[6-(benzyloxy)-2,2-dioxo-2*H*-1,2λ<sup>6</sup>,3-benzoxathiazin-3(4*H*)-yl]ethyl}-4-methylphenyl)-3-{1-[(3*S*)-4-{[*tert*-butyl(dimethyl)silyl]oxy}-3-{[*tert*-butyl(diphenyl)silyl]oxy}butyl]-4-methyl-1*H*-benzotriazol-5-yl}propanoate**

Using General Procedure 6 starting from ethyl (2*E*)-3-{1-[(3*S*)-4-{[*tert*-butyl(dimethyl)silyl]oxy}-3-{[*tert*-butyl(diphenyl)silyl]oxy}butyl]-4-methyl-1*H*-benzotriazol-5-yl}prop-2-enoate (1 eq., 2.87 g, 4.28 mmol) and 6-(benzyloxy)-3-[(1*R*)-1-[2-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]ethyl]-3,4-dihydro-2*H*-1,2λ<sup>6</sup>,3-benzoxathiazine-2,2-dione (1.2 eq., 2.75 g, 5.13 mmol) as reactants, the title compound (3.34 g, 72% yield) was obtained.

<sup>1</sup>H-NMR (500 MHz, DMSO-d<sub>6</sub>, mixture of diastereomers) δ ppm: 7.61-7.06 (m, 20 H), 7.06/7.05 (d/d, 1 H), 7.01/6.99 (dd/dd, 1 H), 6.9/6.85 (d/d, 1 H), 5.27 (m, 1 H), 5.09/5.06 (d+d, 2 H), 4.88/4.87 (t/t, 1 H), 4.66 (m, 2 H), 4.53-4.31 (m, 2 H), 3.92/3.91 (q/q, 2 H), 3.73 (m, 1 H), 3.46-3.36 (m, 2 H), 3.23 (m, 2 H), 2.77 (s, 3 H), 2.28/2.27 (s/s, 3 H), 2.15/2 (m+m, 2 H), 1.42 (d, 3 H), 0.99/0.98 (t/t, 3 H), 0.96/0.94 (s/s, 9 H), 0.68/0.66 (s/s, 9 H), -0.2/-0.21/-0.25/-0.29 (s/s/s/s, 6 H)

**STEP 4 : Preparation of ethyl 3-{1-[(3*S*)-3-{[*tert*-butyl(diphenyl)silyl]oxy}-4-hydroxybutyl]-4-methyl-1*H*-benzotriazol-5-yl}-3-{3-[(1*R*)-1-(6-hydroxy-2,2-dioxo-2*H*-1,2λ<sup>6</sup>,3-benzoxathiazin-3(4*H*)-yl)ethyl]-4-methylphenyl}propanoate**

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Using General Procedure 8 starting from ethyl 3-(3-[(1*R*)-1-[6-(benzyloxy)-2,2-dioxo-2*H*-1,2λ<sup>6</sup>,3-benzoxathiazin-3(4*H*)-yl]ethyl]-4-methylphenyl)-3-{1-[(3*S*)-4-[[*tert*-butyl(dimethyl)silyl]oxy]-3-[[*tert*-butyl(diphenyl)silyl]oxy]butyl]-4-methyl-1*H*-benzotriazol-5-yl}propanoate (1 eq., 3.56 g, 3.29 mmol) as a reactant, the crude ethyl 3-{1-[(3*S*)-4-[[*tert*-butyl(dimethyl)silyl]oxy]-3-[[*tert*-butyl(diphenyl)silyl]oxy]butyl]-4-methyl-1*H*-benzotriazol-5-yl}-3-{3-[(1*R*)-1-(6-hydroxy-2,2-dioxo-2*H*-1,2λ<sup>6</sup>,3-benzoxathiazin-3(4*H*)-yl)ethyl]-4-methylphenyl}propanoate (3.23 g) was obtained. The crude product (1 eq.) was dissolved in EtOH (200 mL) and hydrogen chloride (1*M*, aq.) (2 eq., 7.18 mL, 7.18 mmol) was added. The mixture was stirred at RT for 24h, then the mixture was neutralised with TEA (20 mmol, 2.8 mL) and the solvent was evaporated. The crude product was purified by reversed-phase chromatography using aq. 5 mM NH<sub>4</sub>HCO<sub>3</sub> solution-MeCN as eluents to give the title compound (1.97 g, 62% yield).

<sup>1</sup>**H-NMR** (500 MHz, DMSO-d<sub>6</sub>, mixture of diastereomers) δ ppm: 9.66/9.64 (s/s, 1 H), 7.61-7.02 (m, 15 H), 6.92 (d, 1 H), 6.73 (dd, 1 H), 6.61/6.57 (d/d, 1 H), 5.26 (q, 1 H), 4.89/4.87 (t/t, 1 H), 4.75/4.66 (t/t, 2 H), 4.44-4.25 (m, 2 H), 3.94 (q, 2 H), 3.73 (m, 1 H), 3.38 (m, 2 H), 3.23 (m, 2 H), 2.8/2.77 (s/s, 3 H), 2.28/2.27 (s/s, 3 H), 2.26/2.15/2.02/1.84 (m/m+m/m, 2 H), 1.43/1.41 (d/d, 3 H), 1.01 (t, 3 H), 0.96/0.95/0.87/0.82 (s/s+s/s, 9 H)

**STEP 5 : Preparation of ethyl [(2*R*,19*S*)-19-hydroxy-2,4,31-trimethyl-27,27-dioxo-21,26-dioxa-27λ<sup>6</sup>-thia-1,14,15,16-tetraazahexacyclo[20.5.3.1<sup>3,7</sup>.1<sup>9,13</sup>.0<sup>12,16</sup>.0<sup>25,29</sup>]dotriaconta-3(32),4,6,9(31),10,12,14,22,24,29-decaen-8-yl]acetate**

Using General Procedure 10 starting from ethyl 3-{1-[(3*S*)-3-[[*tert*-butyl(diphenyl)silyl]oxy]-4-hydroxybutyl]-4-methyl-1*H*-benzotriazol-5-yl}-3-{3-[(1*R*)-1-(6-hydroxy-2,2-dioxo-2*H*-1,2λ<sup>6</sup>,3-benzoxathiazin-3(4*H*)-yl)ethyl]-4-methylphenyl}propanoate (1 eq., 1.97 g, 2.24 mmol) as a reactant, the crude ethyl 3-{1-[(3*S*)-3-[[*tert*-butyl(diphenyl)silyl]oxy]-4-chlorobutyl]-4-methyl-1*H*-benzotriazol-5-yl}-3-{3-[(1*R*)-1-(6-hydroxy-2,2-dioxo-2*H*-1,2λ<sup>6</sup>,3-benzoxathiazin-3(4*H*)-yl)ethyl]-4-methylphenyl}propanoate (2.01 g) was obtained. This was reacted without further purification using General Procedure 11 to give the title compound (77 mg, 4% yield).



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**<sup>1</sup>H-NMR** (500 MHz, DMSO-d<sub>6</sub>, mixture of diastereomers) δ ppm: 7.89/7.44 (d/d, 1 H), 7.7/7.69 (d/d, 1 H), 7.44-6.68 (m, 3 H), 7/6.94 (d/d, 1 H), 6.84/6.76 (dd/dd, 1 H), 5.97/5.93 (d/brd, 1 H), 5.39/5.14 (d/d, 1 H), 5.25/5.23 (q/q, 1 H), 4.94/4.74 (t/t, 2 H), 4.92/4.81 (t/t, 1 H), 4.04/4.02/3.41/3.31 (d+d/d+d, 2 H), 3.98/3.25 (m/m, 1 H), 3.95/3.94 (q/q, 2 H), 3.81/3.6/3.57/3.53 (d+d/d+d, 2 H), 3.41/3.33/3.12/3.01 (dd+dd/dd+dd, 2 H), 2.81/2.69 (s/s, 3 H), 2.43/1.99/1.98 (m+m/m, 2 H), 2.32/2.29 (s/s, 3 H), 1.28/1.08 (d/d, 3 H), 1.03/1.02 (t/t, 3 H)

**STEP 6 : Preparation of EXAMPLE 46**

Using General Procedure 12 starting from ethyl [(2*R*,19*S*)-19-hydroxy-2,4,31-trimethyl-27,27-dioxo-21,26-dioxa-27λ<sup>6</sup>-thia-1,14,15,16-tetraazahexacyclo[20.5.3.1<sup>3,7</sup>.1<sup>9,13</sup>.0<sup>12,16</sup>.0<sup>25,29</sup>]dotriaconta-3(32),4,6,9(31),10,12,14,22,24,29-decaen-8-yl]acetate (1 eq., 69 mg, 0.1112 mmol) as a reactant, the title compound (38 mg, 58% yield) was obtained.

The enantiopure products were obtained by chromatographic separation on chiral column.

15

**Example 46a (2*R*,8*S*,19*S*)**

**HRMS** calculated for C<sub>30</sub>H<sub>32</sub>N<sub>4</sub>O<sub>7</sub>S: 592.1992; [M+H]<sup>+</sup> found: 593.2056 (δ = -1.4 ppm)

**<sup>1</sup>H-NMR** (500 MHz, DMSO-d<sub>6</sub>) δ ppm: 7.86 (d, 1 H), 7.67 (d, 1 H), 7.43 (dd, 1 H), 7.18 (d, 1 H), 7.13 (brs., 1 H), 7 (d, 1 H), 6.84 (dd, 1 H), 5.91 (d, 1 H), 5.4 (br., 1 H), 5.23 (q, 1 H), 4.8 (m, 2 H), 4.78 (t, 1 H), 4.03/3.3 (d+d, 2 H), 3.98 (m, 1 H), 3.6/3.52 (dd+dd, 2 H), 3.15/2.93 (dd+dd, 2 H), 2.65 (s, 3 H), 2.28 (s, 3 H), 2 (m, 2 H), 1.25 (d, 3 H)

**<sup>13</sup>C-NMR** (125 MHz, DMSO-d<sub>6</sub>) δ ppm: 131.2, 129.5, 126.2, 125.7, 119.7, 118.5, 109.2, 107.6, 72.8, 66, 55.5, 45, 44, 42.7, 42.2, 35.3, 18.5, 14.4, 13.4

**Example 46b (2*R*,8*R*,19*S*)**

**HRMS** calculated for C<sub>30</sub>H<sub>32</sub>N<sub>4</sub>O<sub>7</sub>S: 592.1992; [M+H]<sup>+</sup> found: 593.2051 (δ = -2.3 ppm)

**<sup>1</sup>H-NMR** (500 MHz, DMSO-d<sub>6</sub>) δ ppm: 7.67 (d, 1 H), 7.46 (d, 1 H), 7.28 (d, 1 H), 7.06 (d, 1 H), 6.94 (d, 1 H), 6.76 (dd, 1 H), 6.68 (brs., 1 H), 5.95 (brs., 1 H), 5.22 (q, 1 H), 5.15 (br., 1 H), 4.94/4.72 (dd+dd, 2 H), 4.91 (br., 1 H), 4.05/3.42 (d+d, 2 H), 3.82/3.6 (d+d, 2 H), 3.26 (br., 1 H), 3.26/2.81 (br+br., 2 H), 2.8 (brs., 3 H), 2.43/2 (br+br., 2 H), 2.31 (s, 3 H), 1.07 (d, 3 H)

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<sup>13</sup>C-NMR (125 MHz, DMSO-d<sub>6</sub>) δ ppm: 131.4, 128.4, 128.1, 125.8, 119.9, 118, 109.2, 108.7, 73.1, 64.2, 55.3, 44.9, 44.4, 40.6, 39.7, 31.1, 18.5, 14.2, 13.3

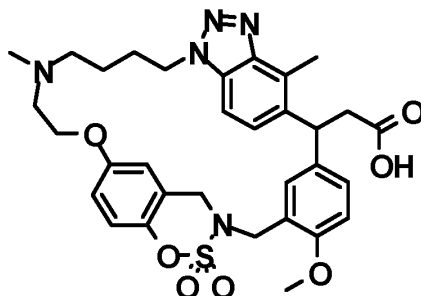
**EXAMPLE 47** : [4-Methoxy-21,34-dimethyl-30,30-dioxo-24,29-dioxa-30λ<sup>6</sup>-thia-

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1,14,15,16,21-

pentaazahexacyclo[23.5.3.1<sup>3,7</sup>.1<sup>9,13</sup>.0<sup>12,16</sup>.0<sup>28,32</sup>]pentatriaconta-

3(35),4,6,9(34),10,12,14,25,27,32-decaen-8-yl]acetic acid



10

**STEP 1** : Preparation of ethyl 3-[1-(4-chlorobutyl)-4-methyl-1*H*-benzotriazol-5-yl]-3-{3-[(6-hydroxy-2,2-dioxo-2*H*-1,2λ<sup>6</sup>,3-benzoxathiazin-3(4*H*)-yl)methyl]-4-methoxyphenyl}propanoate hydrochloride

15 Using General Procedure 10 starting from ethyl 3-[1-(4-hydroxybutyl)-4-methyl-1*H*-benzotriazol-5-yl]-3-{3-[(6-hydroxy-2,2-dioxo-2*H*-1,2λ<sup>6</sup>,3-benzoxathiazin-3(4*H*)-yl)methyl]-4-methoxyphenyl}propanoate (1 eq.) as a reactant, the title compound (yellow solid foam, quant.) was obtained.

<sup>1</sup>H-NMR (500 MHz, DMSO-d<sub>6</sub>) δ ppm: 7.65 (d, 1 H), 7.51 (d, 1 H), 7.26 (d, 1 H), 7.23 (dd, 1 H), 6.89 (d, 1 H), 6.83 (d, 1 H), 6.72 (dd, 1 H), 6.6 (d, 1 H), 4.82 (t, 1 H), 4.7 (t, 2 H), 4.47 (s, 2 H), 4.19 (s, 2 H), 3.93 (q, 2 H), 3.69 (s, 3 H), 3.64 (t, 2 H), 3.14 (d, 2 H), 2.75 (s, 3 H), 1.99 (m, 2 H), 1.68 (m, 2 H), 1 (t, 3 H)

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**STEP 2 : Preparation of ethyl 3-(1-{4-[benzyl(methyl)amino]butyl}-4-methyl-1*H*-benzotriazol-5-yl)-3-{3-[(6-hydroxy-2,2-dioxo-2*H*-1,2λ<sup>6</sup>,3-benzoxathiazin-3(4*H*)-yl)methyl]-4-methoxyphenyl}propanoate**

5 To a stirred solution of ethyl 3-[1-(4-chlorobutyl)-4-methyl-1*H*-benzotriazol-5-yl]-3-{3-[(6-hydroxy-2,2-dioxo-2*H*-1,2λ<sup>6</sup>,3-benzoxathiazin-3(4*H*)-yl)methyl]-4-methoxyphenyl}propanoate hydrochloride (1 eq., 1.2 g, 1.9 mmol) in MeCN (10 mL) *N*-methyl-1-phenylmethanamine (3 eq., 0.68 g, 5.6 mmol) was added at RT and the mixture was heated at 80 °C overnight. The crude product was purified by reversed-phase chromatography using aq.  
10 5 mM NH<sub>4</sub>HCO<sub>3</sub> solution-MeCN as eluents to give the title compound as a beige solid foam (0.82 g, 61 % yield).

<sup>1</sup>H-NMR (500 MHz, DMSO-d<sub>6</sub>) δ ppm: 9.63 (s, 1 H), 7.6 (d, 1 H), 7.49 (d, 1 H), 7.29-7.18 (m, 5 H), 7.26 (d, 1 H), 7.25 (dd, 1 H), 6.88 (d, 1 H), 6.83 (d, 1 H), 6.7 (dd, 1 H), 6.58 (d, 1 H), 4.82 (t, 1 H), 4.64 (t, 2 H), 4.47 (s, 2 H), 4.19 (s, 2 H), 3.93 (q, 2 H), 3.69 (s, 3 H), 3.37 (s, 2 H), 3.14  
15 (d, 2 H), 2.75 (s, 3 H), 2.3 (t, 2 H), 2.01 (s, 3 H), 1.9 (qn, 2 H), 1.41 (qn, 2 H), 1 (t, 3 H)

**STEP 3 : Preparation of ethyl 3-{3-[(6-hydroxy-2,2-dioxo-2*H*-1,2λ<sup>6</sup>,3-benzoxathiazin-3(4*H*)-yl)methyl]-4-methoxyphenyl}-3-{4-methyl-1-[4-(methylamino)butyl]-1*H*-benzotriazol-5-yl}propanoate**

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Using General Procedure 8 starting from ethyl 3-(1-{4-[benzyl(methyl)amino]butyl}-4-methyl-1*H*-benzotriazol-5-yl)-3-{3-[(6-hydroxy-2,2-dioxo-2*H*-1,2λ<sup>6</sup>,3-benzoxathiazin-3(4*H*)-yl)methyl]-4-methoxyphenyl}propanoate (1 eq., 0.83 g, 1.13 mmol) as a reactant, the title compound (white solid foam, 0.4 g, 56% yield) was obtained.

25 <sup>1</sup>H-NMR (500 MHz, DMSO-d<sub>6</sub>) δ ppm: 7.63 (d, 1 H), 7.5 (d, 1 H), 7.25 (d, 1 H), 7.24 (dd, 1 H), 6.89 (d, 1 H), 6.83 (d, 1 H), 6.7 (dd, 1 H), 6.57 (d, 1 H), 4.81 (t, 1 H), 4.64 (t, 2 H), 4.47 (s, 2 H), 4.2/4.17 (d+d, 2 H), 3.94 (q, 2 H), 3.69 (s, 3 H), 3.14 (d, 2 H), 2.75 (s, 3 H), 2.42 (t, 2 H), 2.19 (s, 3 H), 1.89 (qn, 2 H), 1.33 (qn, 2 H), 1.01 (t, 3 H)

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**STEP 4 : Preparation of ethyl [4-methoxy-21,34-dimethyl-30,30-dioxo-24,29-dioxa-30 $\lambda^6$ -thia-1,14,15,16,21-pentaazahexacyclo[23.5.3.1<sup>3,7</sup>.1<sup>9,13</sup>.0<sup>12,16</sup>.0<sup>28,32</sup>]pentatriaconta-3(35),4,6,9(34),10,12,14,25,27,32-decaen-8-yl]acetate**

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To a stirred solution of ethyl 3-{3-[(6-hydroxy-2,2-dioxo-2*H*-1,2 $\lambda^6$ ,3-benzoxathiazin-3(4*H*)-yl)methyl]-4-methoxyphenyl}-3-{4-methyl-1-[4-(methylamino)butyl]-1*H*-benzotriazol-5-yl}propanoate (1 eq., 0.286 g, 0.448 mmol) in MeCN (6 mL) Cs<sub>2</sub>CO<sub>3</sub> (5 eq., 0.73 g, 2.24 mmol) and 1,2-dibromoethane (5 eq., 0.193 mL, 2.24 mmol) were added at RT and the mixture was heated at 80 °C for 5 h. The crude product was purified by reversed-phase chromatography using aq. 5 mM NH<sub>4</sub>HCO<sub>3</sub> solution-MeCN eluents to give the title compound as a white solid (0.045 g, 15 % yield).

<sup>1</sup>H-NMR (500 MHz, DMSO-d<sub>6</sub>)  $\delta$  ppm: 7.63 (d, 1 H), 7.55 (d, 1 H), 7.44 (dd, 1 H), 7.14 (d, 1 H), 7.07 (d, 1 H), 7 (dd, 1 H), 6.96 (d, 1 H), 6.47 (d, 1 H), 4.8 (t, 1 H), 4.76/4.69 (m+m, 2 H), 4.37/3.96 (d+d, 2 H), 4.27/3.92 (d+d, 2 H), 4.12/4.05 (m+m, 2 H), 3.89 (q, 2 H), 3.77 (s, 3 H), 3.14/3.07 (dd+dd, 2 H), 2.76 (s, 3 H), 2.73/2.7 (m+m, 2 H), 2.59/2.42 (m+m, 2 H), 2.22 (s, 3 H), 1.96 (qn, 2 H), 1.63 (m, 2 H), 0.98 (t, 3 H)

**STEP 5 : Preparation of EXAMPLE 47**

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Using General Procedure 12 starting from ethyl [4-methoxy-21,34-dimethyl-30,30-dioxo-24,29-dioxa-30 $\lambda^6$ -thia-1,14,15,16,21-pentaazahexacyclo[23.5.3.1<sup>3,7</sup>.1<sup>9,13</sup>.0<sup>12,16</sup>.0<sup>28,32</sup>]pentatriaconta-3(35),4,6,9(34),10,12,14,25,27,32-decaen-8-yl]acetate (1 eq., 41 mg, 0.0617 mmol) as a reactant, the title compound (white solid, 35 mg, 89% yield) was obtained.

<sup>25</sup> **HRMS** calculated for C<sub>32</sub>H<sub>37</sub>N<sub>5</sub>O<sub>7</sub>S: 635.2414; [M+H]<sup>+</sup> found = 636.2479 ( $\delta$  = -1.2 ppm)

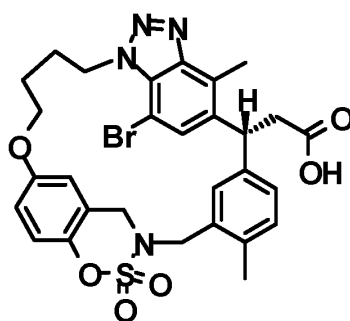
<sup>1</sup>H-NMR (500 MHz, DMSO-d<sub>6</sub>)  $\delta$  ppm 12.42 (brs, 1 H), 7.64 (d, 1 H), 7.54 (d, 1 H), 7.45 (dd, 1 H), 7.11 (d, 1 H), 7.07 (d, 1 H), 7 (dd, 1 H), 6.96 (d, 1 H), 6.45 (d, 1 H), 4.78 (t, 1 H), 4.76/4.7 (m+m, 2 H), 4.36/3.97 (d+d, 2 H), 4.27/3.91 (d+d, 2 H), 4.13/4.05 (m+m, 2 H), 3.77 (s, 3 H), 3.03/2.98 (dd+dd, 2 H), 2.75 (s, 3 H), 2.74/2.69 (m+m, 2 H), 2.6/2.43 (m+m, 2 H), 2.23 (s, 3 H), 1.96 (m, 2 H), 1.63 (m, 2 H)

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<sup>13</sup>C-NMR (125 MHz, DMSO-d<sub>6</sub>) δ ppm: 131.2, 130.9, 126.8, 119.1, 114.5, 114.4, 111.7, 108, 66.7, 56.6, 56.2, 56.2, 48.6, 48.6, 47.5, 42.6, 41, 41, 27.3, 23.4, 13.3

**EXAMPLE 48 :** [(8*R*)-11-Bromo-4,31-dimethyl-27,27-dioxo-21,26-dioxa-27λ<sup>6</sup>-thia-1,14,15,16-tetraazahexacyclo[20.5.3.1<sup>3,7</sup>.1<sup>9,13</sup>.0<sup>12,16</sup>.0<sup>25,29</sup>]dotriaconta-3(32),4,6,9(31),10,12,14,22,24,29-decaen-8-yl]acetic acid



**STEP 1 :** Preparation of ethyl [(8*R*)-11-bromo-4,31-dimethyl-27,27-dioxo-21,26-dioxa-27λ<sup>6</sup>-thia-1,14,15,16-tetraazahexacyclo[20.5.3.1<sup>3,7</sup>.1<sup>9,13</sup>.0<sup>12,16</sup>.0<sup>25,29</sup>]dotriaconta-3(32),4,6,9(31),10,12,14,22,24,29-decaen-8-yl]acetate

To a stirred solution of ethyl [(8*R*)-4,31-dimethyl-27,27-dioxo-21,26-dioxa-27λ<sup>6</sup>-thia-1,14,15,16-tetraazahexacyclo[20.5.3.1<sup>3,7</sup>.1<sup>9,13</sup>.0<sup>12,16</sup>.0<sup>25,29</sup>]dotriaconta-3(32),4,6,9(31),10,12,14,22,24,29-decaen-8-yl]acetate (1 eq., 1.47 g, 2.49 mmol) in nitromethane (15 mL) potassium peroxymonosulfate (3 eq., 3.595 g, 7.466 mmol) and potassium bromide (0.77 eq., 0.23 g, 1.93 mmol) were added at RT, then the mixture was stirred at 60 °C for 2 days. The reaction mixture was taken up in EtOAc (150 ml) and the organic layer was washed with 10% aq. Na<sub>2</sub>S<sub>2</sub>O<sub>3</sub> solution (150 ml). The organic layer was dried over anhydrous MgSO<sub>4</sub>, filtered and concentrated under reduced pressure. The residue was purified by normal phase silica gel chromatography using heptane-EtOAc gradient elution to give the title compound as a white solid (0.63 g, 38% yield).

<sup>1</sup>H-NMR (500 MHz, DMSO-d<sub>6</sub>) δ ppm: 7.63 (s, 1 H), 7.49 (dd, 1 H), 7.3 (d, 1 H), 7 (d, 1 H), 6.81 (dd, 1 H), 6.5 (d, 1 H), 5.73 (d, 1 H), 5.18/4.82 (dm+m, 2 H), 4.74 (m, 1 H), 4.27/3.83 (d+d,

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2 H), 4.04/3.76 (d+d, 2 H), 3.95 (m, 2 H), 3.58/3.12 (dt+m, 2 H), 3.11 (m, 2 H), 2.59 (s, 3 H), 2.33 (s, 3 H), 2.27/2.17 (m+m, 2 H), 1.91/1.68 (m+m, 2 H), 1.03 (t, 3 H)

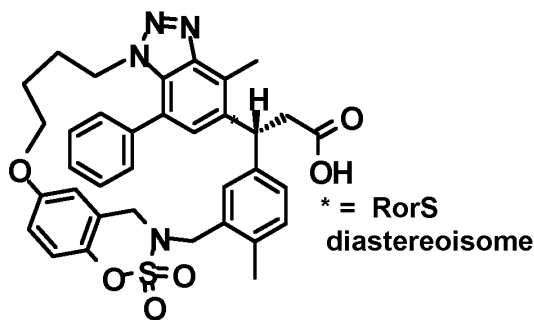
## STEP 2 : Preparation of EXAMPLE 48

5

Using General Procedure 12 starting from ethyl [(8*R*)-11-bromo-4,31-dimethyl-27,27-dioxo-21,26-dioxa-27λ<sup>6</sup>-thia-1,14,15,16-tetraazahexacyclo[20.5.3.1<sup>3,7</sup>.1<sup>9,13</sup>.0<sup>12,16</sup>.0<sup>25,29</sup>]dotriaconta-3(32),4,6,9(31),10,12,14,22,24,29-decaen-8-yl]acetate (1 eq., 308 mg, 0.46 mmol) as a reactant, the title compound (white solid, 144 mg, 49% yield) was obtained.

10 <sup>1</sup>H-NMR (500 MHz, DMSO-d<sub>6</sub>) δ ppm: 12.28 (brs, 1 H), 7.6 (s, 1 H), 7.5 (dd, 1 H), 7.3 (d, 1 H), 7 (d, 1 H), 6.81 (dd, 1 H), 6.49 (d, 1 H), 5.73 (d, 1 H), 5.19/4.82 (m+m, 2 H), 4.82 (t, 1 H), 4.26/3.84 (d+d, 2 H), 4.03/3.77 (d+d, 2 H), 3.58/3.13 (m+m, 2 H), 3 (d, 2 H), 2.59 (s, 3 H), 2.33 (s, 3 H), 2.27/2.18 (m+m, 2 H), 1.91/1.69 (qn+qn, 2 H)

15 **EXAMPLE 49** : [(8*R*)-4,31-Dimethyl-27,27-dioxo-11-phenyl-21,26-dioxa-27λ<sup>6</sup>-thia-1,14,15,16-tetraazahexacyclo[20.5.3.1<sup>3,7</sup>.1<sup>9,13</sup>.0<sup>12,16</sup>.0<sup>25,29</sup>]dotriaconta-3(32),4,6,9(31),10,12,14,22,24,29-decaen-8-yl]acetic acid



20 **STEP 1** : Preparation of ethyl [(8*R*)-4,31-dimethyl-27,27-dioxo-11-phenyl-21,26-dioxa-27λ<sup>6</sup>-thia-1,14,15,16-tetraazahexacyclo[20.5.3.1<sup>3,7</sup>.1<sup>9,13</sup>.0<sup>12,16</sup>.0<sup>25,29</sup>]dotriaconta-3(32),4,6,9(31),10,12,14,22,24,29-decaen-8-yl]acetate

A mixture of ethyl [(8*R*)-11-bromo-4,31-dimethyl-27,27-dioxo-21,26-dioxa-27λ<sup>6</sup>-thia-1,14,15,16-tetraazahexacyclo[20.5.3.1<sup>3,7</sup>.1<sup>9,13</sup>.0<sup>12,16</sup>.0<sup>25,29</sup>]dotriaconta-

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3(32),4,6,9(31),10,12,14,22,24,29-decaen-8-yl]acetate (1 eq., 300 g, 0.448 mmol), phenylboronic acid (3 eq., 164 mg, 1.344 mmol), Cs<sub>2</sub>CO<sub>3</sub> (3 eq., 438 mg, 1.344 mmol), A<sup>ta</sup>phos.PdCl<sub>2</sub> catalyst (0.1 eq., 20 mg, 0.0448 mmol), THF (4 mL) and water (4 mL) was heated in a microwave reactor at 100 °C for 1 h under nitrogen atmosphere. After the mixture was cooled down, the layers were separated, the aq. layer was extracted with further 2x5 ml of EtOAc. The combined organic layer was dried over MgSO<sub>4</sub>, evaporated under reduced pressure. The crude product contains the mixture of 2 atropisomers (ratio: 94:6). The residue was purified by reversed-phase chromatography using aq. 5 mM NH<sub>4</sub>HCO<sub>3</sub> solution-MeCN eluents to give the title compound as a white solid (diastereomer1, 232 mg, 78% yield).

**<sup>1</sup>H-NMR** (500 MHz, DMSO-d<sub>6</sub>) δ ppm: 7.49 (dd, 1 H), 7.47 (t, 1 H), 7.45 (t, 2 H), 7.31 (s, 1 H), 7.28 (d, 1 H), 7.21 (br., 2 H), 7.08 (d, 1 H), 6.83 (d, 1 H), 6.8 (dd, 1 H), 5.82 (d, 1 H), 4.79 (t, 1 H), 4.77/4.32 (dd+dt, 2 H), 4.39/3.95 (d+d, 2 H), 4.13/3.83 (d+d, 2 H), 3.86 (q, 2 H), 3.35/2.95 (m+m, 2 H), 3.06 (d, 2 H), 2.72 (s, 3 H), 2.35 (s, 3 H), 1.43/1.1 (m+m, 2 H), 1.35/1.1 (m+m, 2 H), 0.9 (t, 3 H)

## STEP 2 : Preparation of EXAMPLE 49

Using General Procedure 12 starting from ethyl [(8*R*)-4,31-dimethyl-27,27-dioxo-11-phenyl-21,26-dioxa-27λ<sup>6</sup>-thia-1,14,15,16-tetraazahexacyclo[20.5.3.1<sup>3,7</sup>.1<sup>9,13</sup>.0<sup>12,16</sup>.0<sup>25,29</sup>]dotriaconta-3(32),4,6,9(31),10,12,14,22,24,29-decaen-8-yl]acetate (1 eq., 228 mg, 0.342 mmol) as a reactant, the title compound (white solid, 193 mg, 88% yield) was obtained.

**HRMS** calculated for C<sub>35</sub>H<sub>34</sub>N<sub>4</sub>O<sub>6</sub>S: 638.2199; [M+H]<sup>+</sup> found: 639.2263 (δ = -1.4 ppm)

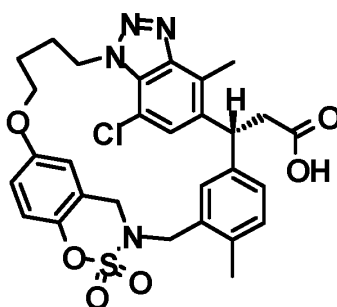
**<sup>1</sup>H-NMR** (500 MHz, DMSO-d<sub>6</sub>) δ ppm: 12.11 (brs, 1 H), 7.49 (dd, 1 H), 7.47 (t, 1 H), 7.45 (t, 2 H), 7.29 (s, 1 H), 7.28 (d, 1 H), 7.22 (br, 2 H), 7.08 (d, 1 H), 6.82 (d, 1 H), 6.79 (dd, 1 H), 5.83 (d, 1 H), 4.77/4.33 (m+m, 2 H), 4.77 (t, 1 H), 4.38/3.97 (d+d, 2 H), 4.12/3.85 (d+d, 2 H), 3.34/2.97 (m+m, 2 H), 2.96 (d, 2 H), 2.73 (s, 3 H), 2.35 (s, 3 H), 1.43/1.08 (m+m, 2 H), 1.34/1.08 (m+m, 2 H)

**<sup>13</sup>C-NMR** (125 MHz, DMSO-d<sub>6</sub>) δ ppm: 173.1, 155.9, 147.3, 144.4, 141.7, 137.8, 136.8, 136.4, 132, 131.3, 131.3, 129.3, 129, 128.8, 128.6, 127.9, 127, 123.8, 119.6, 117.8, 117.1, 110.2, 67.4, 52.4, 50.5, 48.8, 41.6, 41.2, 25.6, 24.1, 18.6, 13.3

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**EXAMPLE 50 :** [(8*R*)-11-Chloro-4,31-dimethyl-27,27-dioxo-21,26-dioxa-27 $\lambda^6$ -thia-1,14,15,16-tetraazahexacyclo[20.5.3.1<sup>3,7</sup>.1<sup>9,13</sup>.0<sup>12,16</sup>.0<sup>25,29</sup>]dotriaconta-3(32),4,6,9(31),10,12,14,22,24,29-decaen-8-yl]acetic acid

5



**STEP 1:** Preparation of ethyl [(8*R*)-11-chloro-4,31-dimethyl-27,27-dioxo-21,26-dioxa-27 $\lambda^6$ -thia-1,14,15,16-tetraazahexacyclo[20.5.3.1<sup>3,7</sup>.1<sup>9,13</sup>.0<sup>12,16</sup>.0<sup>25,29</sup>]dotriaconta-3(32),4,6,9(31),10,12,14,22,24,29-decaen-8-yl]acetate and ethyl [(8*R*)-11,30-dichloro-4,31-dimethyl-27,27-dioxo-21,26-dioxa-27 $\lambda^6$ -thia-1,14,15,16-tetraazahexacyclo[20.5.3.1<sup>3,7</sup>.1<sup>9,13</sup>.0<sup>12,16</sup>.0<sup>25,29</sup>]dotriaconta-3(32),4,6,9(31),10,12,14,22,24,29-decaen-8-yl]acetate and ethyl [(8*R*)-11,23-dichloro-4,31-dimethyl-27,27-dioxo-21,26-dioxa-27 $\lambda^6$ -thia-1,14,15,16-tetraazahexacyclo[20.5.3.1<sup>3,7</sup>.1<sup>9,13</sup>.0<sup>12,16</sup>.0<sup>25,29</sup>]dotriaconta-3(32),4,6,9(31),10,12,14,22,24,29-decaen-8-yl]acetate

To a stirred solution of ethyl [(8*R*)-4,31-dimethyl-27,27-dioxo-21,26-dioxa-27 $\lambda^6$ -thia-1,14,15,16-tetraazahexacyclo[20.5.3.1<sup>3,7</sup>.1<sup>9,13</sup>.0<sup>12,16</sup>.0<sup>25,29</sup>]dotriaconta-3(32),4,6,9(31),10,12,14,22,24,29-decaen-8-yl]acetate (1 eq., 0.5 g, 0.846 mmol) in nitromethane (10 mL) potassium peroxydisulfate (3 eq., 1.223 g, 2.54 mmol) and potassium chloride (1.5 eq., 95 mg, 1.269 mmol) were added at RT, then the mixture was stirred at 60 °C for 24 h. The reaction mixture was diluted with DCM (20 ml) and the organic layer was washed with water (20 ml). The organic layer was dried over anhydrous MgSO<sub>4</sub>, filtered and evaporated



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under reduced pressure. The residue was purified by reversed-phase chromatography using aq. 5 mM HCOOH solution-MeCN eluents to give the 3 title compounds:

- Ethyl [(8*R*)-11-chloro-4,31-dimethyl-27,27-dioxo-21,26-dioxa-27 $\lambda^6$ -thia-1,14,15,16-tetraazahexacyclo[20.5.3.1<sup>3,7</sup>.1<sup>9,13</sup>.0<sup>12,16</sup>.0<sup>25,29</sup>]dotriaconta-**  
5 **3(32),4,6,9(31),10,12,14,22,24,29-decaen-8-yl]acetate** (61 mg, 12 % yield),  
<sup>1</sup>H-NMR (500 MHz, DMSO-d<sub>6</sub>)  $\delta$  ppm: 7.52 (s, 1 H), 7.49 (dd, 1 H), 7.3 (d, 1 H), 7 (d, 1 H), 6.82 (dd, 1 H), 6.53 (d, 1 H), 5.76 (d, 1 H), 5.1/4.89 (m+m, 2 H), 4.75 (t, 1 H), 4.3/3.83 (d+d, 2 H), 4.05/3.76 (d+d, 2 H), 3.95 (q, 2 H), 3.61/3.17 (t+t, 2 H), 3.12 (dd, 2 H), 2.61 (s, 3 H), 2.33  
10 (s, 3 H), 2.22/2.14 (m, 2 H), 1.9/1.67 (m, 2 H), 1.03 (t, 3 H)
- Ethyl [(8*R*)-11,30-dichloro-4,31-dimethyl-27,27-dioxo-21,26-dioxa-27 $\lambda^6$ -thia-1,14,15,16-tetraazahexacyclo[20.5.3.1<sup>3,7</sup>.1<sup>9,13</sup>.0<sup>12,16</sup>.0<sup>25,29</sup>]dotriaconta-**  
15 **3(32),4,6,9(31),10,12,14,22,24,29-decaen-8-yl]acetate** (74 mg),  
<sup>1</sup>H-NMR (500 MHz, DMSO-d<sub>6</sub>)  $\delta$  ppm: 7.48 (dd, 1 H), 7.34 (s, 1 H), 7.33 (d, 1 H), 7.11 (d, 1 H), 7.05 (d, 1 H), 6.43 (d, 1 H), 5.07/4.85 (dm+m, 2 H), 4.74 (dd, 1 H), 4.27/4 (d+d, 2 H), 4.09/3.87 (d+d, 2 H), 4.04/3.78 (m+m, 2 H), 3.91 (q, 2 H), 3.27/3.09 (dd+dd, 2 H), 2.62 (s, 3 H), 2.43/2.12 (m+m, 2 H), 2.34 (s, 3 H), 1.74/1.43 (m+m, 2 H), 0.98 (t, 3 H)
- 20 **Ethyl [(8*R*)-11,23-dichloro-4,31-dimethyl-27,27-dioxo-21,26-dioxa-27 $\lambda^6$ -thia-1,14,15,16-tetraazahexacyclo[20.5.3.1<sup>3,7</sup>.1<sup>9,13</sup>.0<sup>12,16</sup>.0<sup>25,29</sup>]dotriaconta-**  
**3(32),4,6,9(31),10,12,14,22,24,29-decaen-8-yl]acetate** (42 mg).  
<sup>1</sup>H-NMR (500 MHz, DMSO-d<sub>6</sub>)  $\delta$  ppm: 7.57 (s, 1 H), 7.48 (dd, 1 H), 7.36 (s, 1 H), 7.27 (d, 1 H), 6.66 (d, 1 H), 6.02 (s, 1 H), 5.09/4.93 (m+m, 2 H), 4.73 (t, 1 H), 4.44/3.78 (d+d, 2 H),  
25 4.09/3.65 (d+d, 2 H), 3.97/3.93 (m+m, 2 H), 3.6/3.04 (m+m, 2 H), 3.15/3.04 (dd+dd, 2 H), 2.62 (s, 3 H), 2.32 (s, 3 H), 2.28/2.08 (m+m, 2 H), 1.9/1.67 (m+m, 2 H), 1.03 (t, 3 H)

**STEP 2 : Preparation of EXAMPLE 50**

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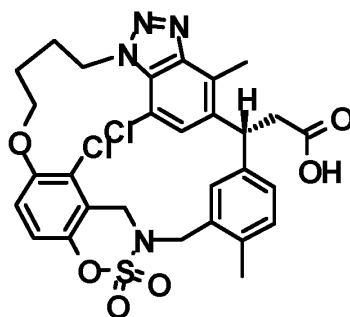
Using General Procedure 12 starting from ethyl [(8*R*)-11-chloro-4,31-dimethyl-27,27-dioxo-21,26-dioxa-27 $\lambda^6$ -thia-1,14,15,16-tetraazahexacyclo[20.5.3.1<sup>3,7</sup>.1<sup>9,13</sup>.0<sup>12,16</sup>.0<sup>25,29</sup>]dotriaconta-3(32),4,6,9(31),10,12,14,22,24,29-decaen-8-yl]acetate (1 eq., 54 mg, 0.086 mmol) as a reactant, the title compound (white solid, 26 mg, 50% yield) was obtained.

5 **HRMS** calculated for C<sub>29</sub>H<sub>29</sub>ClN<sub>4</sub>O<sub>6</sub>S: 596.1496; [M+H]<sup>+</sup> found: 597.156 ( $\delta$  = -1.5 ppm)

**<sup>1</sup>H-NMR** (500 MHz, DMSO-d<sub>6</sub>)  $\delta$  ppm: 7.5 (dd, 1 H), 7.49 (s, 1 H), 7.29 (d, 1 H), 7 (d, 1 H), 6.81 (dd, 1 H), 6.5 (d, 1 H), 5.74 (d, 1 H), 5.09/4.87 (m+m, 2 H), 4.72 (t, 1 H), 4.28/3.83 (d+d, 2 H), 4.04/3.76 (d+d, 2 H), 3.6/3.17 (dm+dm, 2 H), 3.02/2.98 (dd+dd, 2 H), 2.6 (s, 3 H), 2.33 (s, 3 H), 2.22/2.15 (m+m, 2 H), 1.9/1.68 (m+m, 2 H)

10 **<sup>13</sup>C-NMR** (125 MHz, DMSO-d<sub>6</sub>)  $\delta$  ppm: 131.4, 131.1, 129, 127.6, 119.5, 117.1, 111.3, 67.9, 51.9, 50, 48.7, 41.6, 40.8, 26.5, 26.3, 18.5, 13.3

**EXAMPLE 51** : [(8*R*)-11,30-Dichloro-4,31-dimethyl-27,27-dioxo-21,26-dioxa-27 $\lambda^6$ -thia-1,14,15,16-tetraazahexacyclo[20.5.3.1<sup>3,7</sup>.1<sup>9,13</sup>.0<sup>12,16</sup>.0<sup>25,29</sup>]dotriaconta-3(32),4,6,9(31),10,12,14,22,24,29-decaen-8-yl]acetic acid



Using General Procedure 12 starting from ethyl [(8*R*)-11,30-dichloro-4,31-dimethyl-27,27-dioxo-21,26-dioxa-27 $\lambda^6$ -thia-1,14,15,16-tetraazahexacyclo[20.5.3.1<sup>3,7</sup>.1<sup>9,13</sup>.0<sup>12,16</sup>.0<sup>25,29</sup>]

20 dotriaconta-3(32),4,6,9(31),10,12,14,22,24,29-decaen-8-yl]acetate (1 eq., 69 mg, 0.1046 mmol) as a reactant, the title compound (white solid, 57 mg, 86% yield) was obtained.

**HRMS** calculated for C<sub>29</sub>H<sub>28</sub>Cl<sub>2</sub>N<sub>4</sub>O<sub>6</sub>S: 630.1107; [M+H]<sup>+</sup> found: 631.1179 ( $\delta$  = -0.1 ppm)

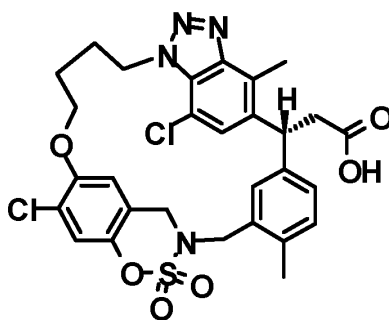
-255-

**<sup>1</sup>H-NMR** (500 MHz, DMSO-d<sub>6</sub>) δ ppm: 7.49 (dd, 1 H), 7.32 (d, 1 H), 7.3 (s, 1 H), 7.11 (d, 1 H), 7.04 (d, 1 H), 6.43 (d, 1 H), 5.07/4.85 (dm+m, 2 H), 4.72 (t, 1 H), 4.27/4 (d+d, 2 H), 4.09/3.87 (d+d, 2 H), 4.03/3.76 (m+m, 2 H), 3.17/2.96 (dd+dd, 2 H), 2.62 (s, 3 H), 2.44/2.13 (m+m, 2 H), 2.34 (s, 3 H), 1.74/1.45 (m+m, 2 H)

5 **<sup>13</sup>C-NMR** (125 MHz, DMSO-d<sub>6</sub>) δ ppm: 131.5, 131.5, 127.7, 127.6, 117.6, 117.6, 70.3, 52.6, 49.9, 47.4, 40.3, 39.8, 27.2, 26.7, 18.5, 13.2

**EXAMPLE 52** : [(8*R*)-11,23-Dichloro-4,31-dimethyl-27,27-dioxo-21,26-dioxa-27λ<sup>6</sup>-thia-1,14,15,16-tetraazahexacyclo[20.5.3.1<sup>3,7</sup>.1<sup>9,13</sup>.0<sup>12,16</sup>.0<sup>25,29</sup>]dotriaconta-3(32),4,6,9(31),10,12,14,22,24,29-decaen-8-yl]acetic acid

10



Using General Procedure 12 starting from ethyl [(8*R*)-11,23-dichloro-4,31-dimethyl-27,27-dioxo-21,26-dioxa-27λ<sup>6</sup>-thia-1,14,15,16-tetraazahexacyclo[20.5.3.1<sup>3,7</sup>.1<sup>9,13</sup>.0<sup>12,16</sup>.0<sup>25,29</sup>]

15 dotriaconta-3(32),4,6,9(31),10,12,14,22,24,29-decaen-8-yl]acetate (1 eq., 38 mg, 0.0576 mmol) as a reactant, the title compound (white solid, 23 mg, 63% yield) was obtained.

**HRMS** calculated for C<sub>29</sub>H<sub>28</sub>Cl<sub>2</sub>N<sub>4</sub>O<sub>6</sub>S: 630.1107; [M+H]<sup>+</sup> found: 631.1173 (δ = -1.0 ppm)

**<sup>1</sup>H-NMR** (500 MHz, DMSO-d<sub>6</sub>) δ ppm: 7.55 (s, 1 H), 7.49 (dd, 1 H), 7.36 (s, 1 H), 7.27 (d, 1 H), 6.64 (d, 1 H), 6.01 (s, 1 H), 5.09/4.93 (m+m, 2 H), 4.71 (t, 1 H), 4.43/3.78 (d+d, 2 H), 4.09/3.66 (d+d, 2 H), 3.6/3.04 (m+m, 2 H), 3.04/2.94 (dd+dd, 2 H), 2.61 (s, 3 H), 2.32 (s, 3 H), 2.28/2.08 (m+m, 2 H), 1.9/1.66 (m+m, 2 H)

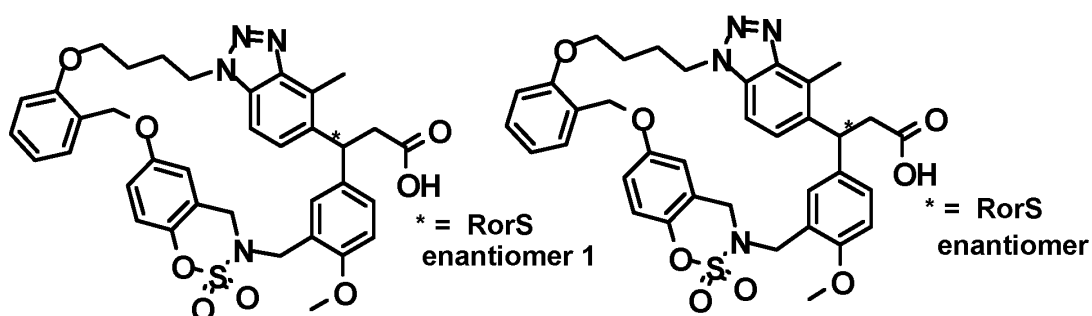
20

**<sup>13</sup>C-NMR** (125 MHz, DMSO-d<sub>6</sub>) δ ppm: 151.4, 131.3, 131.1, 129.3, 127.5, 120, 111.4, 68.5, 52, 49.8, 48.7, 41.9, 40.8, 26.2, 26, 18.5, 13.4

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**EXAMPLE 53 :** [4-Methoxy-39-methyl-35,35-dioxo-21,29,34-trioxa-35 $\lambda^6$ -thia-1,14,15,16-tetraazaheptacyclo[28.5.3.1<sup>3,7</sup>.1<sup>9,13</sup>.0<sup>12,16</sup>.0<sup>22,27</sup>.0<sup>33,37</sup>]tetraconta-3(40),4,6,9(39),10,12,14,22,24,26,30,32,37-tridecaen-8-yl]acetic acid

5



**STEP 1 :** Preparation of ethyl 3-{1-[4-(2-formylphenoxy)butyl]-4-methyl-1*H*-benzotriazol-5-yl}-3-{3-[(6-hydroxy-2,2-dioxo-2*H*-1,2 $\lambda^6$ ,3-benzoxathiazin-3(4*H*)-yl)methyl]-4-methoxyphenyl}propanoate

10

Ethyl 3-[1-(4-chlorobutyl)-4-methyl-1*H*-benzotriazol-5-yl]-3-{3-[(6-hydroxy-2,2-dioxo-2*H*-1,2 $\lambda^6$ ,3-benzoxathiazin-3(4*H*)-yl)methyl]-4-methoxyphenyl}propanoate hydrochloride (1 eq., 0.5 g, 0.78 mmol) was dissolved in dry DMF (8 mL) and 2-hydroxybenzaldehyde (24 eq., 2 mL, 19 mmol) was added followed by addition of Cs<sub>2</sub>CO<sub>3</sub> (0.50 g, 1.5 mmol). The reaction mixture was stirred at 120°C for 1h under N<sub>2</sub> atmosphere. After 1h an additional 0.5 g (1.5 mmol) of Cs<sub>2</sub>CO<sub>3</sub> was added and the mixture was stirred for additional 2h at 120°C. The mixture was cooled to RT, poured on ice and extracted with DCM. The collected organic layer was dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and evaporated under reduced pressure. The crude product was purified by normal phase silica gel chromatography using DCM-MeOH (100:0 to 97.5:2.5) as eluents resulted in 0.426 g (75% yield) of the title compound as a light brown foamy material.

20

**<sup>1</sup>H-NMR** (500 MHz, DMSO-*d*<sub>6</sub>)  $\delta$  ppm: 10.32 (s, 1 H), 9.62 (s, 1 H), 7.66 (d, 1 H), 7.66 (dd, 1 H), 7.6 (ddd, 1 H), 7.5 (d, 1 H), 7.26 (d, 1 H), 7.23 (dd, 1 H), 7.16 (d, 1 H), 7.04 (t, 1 H), 6.89 (d, 1 H), 6.83 (d, 1 H), 6.7 (dd, 1 H), 6.58 (d, 1 H), 4.81 (t, 1 H), 4.75 (t, 2 H), 4.48 (s, 2 H),

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4.21/4.17 (d+d, 2 H), 4.13 (t, 2 H), 3.94 (q, 2 H), 3.69 (s, 3 H), 3.14 (d, 2 H), 2.75 (s, 3 H), 2.1 (m, 2 H), 1.74 (m, 2 H), 1.01 (t, 3 H)

**STEP 2 : Preparation of ethyl 3-{3-[(6-hydroxy-2,2-dioxo-2*H*-1,2λ<sup>6</sup>,3-benzoxathiazin-3(4*H*)-yl)methyl]-4-methoxyphenyl}-3-(1-{4-[2-(hydroxymethyl)phenoxy]butyl}-4-methyl-1*H*-benzotriazol-5-yl)propanoate**

Ethyl 3-{1-[4-(2-formylphenoxy)butyl]-4-methyl-1*H*-benzotriazol-5-yl}-3-{3-[(6-hydroxy-2,2-dioxo-2*H*-1,2λ<sup>6</sup>,3-benzoxathiazin-3(4*H*)-yl)methyl]-4-methoxyphenyl}propanoate (1 eq., 0.350 g, 0.480 mmol) was dissolved in EtOH (2 mL) and sodium borohydride (2.75 eq., 50 mg, 1.322 mmol) was added. The reaction mixture was stirred at RT for 1 h. The mixture was poured on crushed ice and evaporated under reduced pressure. The residue was partitioned between water and EtOAc, the phases were separated and the aq. phase was extracted with additional portions of EtOAc. The combined organic phase was dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and evaporated to Celite. The crude product was purified by normal phase silica gel chromatography using DCM-MeOH (100:0 to 95.2:4.8) as an eluent, resulting in 0.33 g (94% yield) of the title compound as an off-white foamy material.

<sup>1</sup>H-NMR (500 MHz, DMSO-d<sub>6</sub>) δ ppm: 9.62 (s, 1 H), 7.66 (d, 1 H), 7.51 (d, 1 H), 7.35 (d, 1 H), 7.26 (d, 1 H), 7.23 (dd, 1 H), 7.15 (t, 1 H), 6.9 (t, 1 H), 6.89 (d, 1 H), 6.87 (d, 1 H), 6.84 (d, 1 H), 6.71 (dd, 1 H), 6.59 (d, 1 H), 4.94 (t, 1 H), 4.82 (t, 1 H), 4.73 (t, 2 H), 4.6 (d, 2 H), 4.48 (s, 2 H), 4.19 (s, 2 H), 3.96 (t, 2 H), 3.94 (q, 2 H), 3.69 (s, 3 H), 3.15 (d, 2 H), 2.76 (s, 3 H), 2.06 (m, 2 H), 1.68 (m, 2 H), 1.01 (t, 3 H)

**STEP 3 : Preparation of ethyl 3-(1-{4-[2-(chloromethyl)phenoxy]butyl}-4-methyl-1*H*-benzotriazol-5-yl)-3-{3-[(6-hydroxy-2,2-dioxo-2*H*-1,2λ<sup>6</sup>,3-benzoxathiazin-3(4*H*)-yl)methyl]-4-methoxyphenyl}propanoate**

Ethyl 3-{3-[(6-hydroxy-2,2-dioxo-2*H*-1,2λ<sup>6</sup>,3-benzoxathiazin-3(4*H*)-yl)methyl]-4-methoxyphenyl}-3-(1-{4-[2-(hydroxymethyl)phenoxy]butyl}-4-methyl-1*H*-benzotriazol-5-yl)propanoate (1 eq., 0.330 g, 0.452 mmol) was dissolved in dry DCM (2 mL) and the mixture

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was cooled to 0°C. Thionyl chloride (70 µL, 0.95965 mmol) was added and the reaction mixture was stirred at 0°C for 30 minutes. After completion of the reaction the volatiles were evaporated to dryness, the excess of the reagent was removed by evaporation of DCM from the residue. Drying of the crude product in high vacuo at RT resulted in 0.441 g (quant.) of a title compound as an off-white foamy material.

**<sup>1</sup>H-NMR** (500 MHz, DMSO-d<sub>6</sub>) δ ppm: 9.66 (brs, 1 H), 7.66 (d, 1 H), 7.5 (d, 1 H), 7.35 (dm, 1 H), 7.29 (m, 1 H), 7.26 (d, 1 H), 7.23 (dd, 1 H), 6.97 (dm, 1 H), 6.9 (m, 1 H), 6.89 (d, 1 H), 6.84 (d, 1 H), 6.71 (dd, 1 H), 6.59 (d, 1 H), 4.82 (t, 1 H), 4.75 (t, 2 H), 4.64 (s, 2 H), 4.48 (s, 2 H), 4.19 (s, 2 H), 4.04 (t, 2 H), 3.93 (q, 2 H), 3.69 (s, 3 H), 3.15 (d, 2 H), 2.75 (s, 3 H), 2.1 (m, 2 H), 1.71 (m, 2 H), 1 (t, 3 H)

**STEP 4 : Preparation of ethyl [4-methoxy-39-methyl-35,35-dioxo-21,29,34-trioxa-35λ<sup>6</sup>-thia-1,14,15,16-tetraazaheptacyclo[28.5.3.1<sup>3,7</sup>.1<sup>9,13</sup>.0<sup>12,16</sup>.0<sup>22,27</sup>.0<sup>33,37</sup>]tetraconta-3(40),4,6,9(39),10,12,14,22,24,26,30,32,37-tridecaen-8-yl]acetate**

Using General Procedure 11 starting from ethyl 3-(1-{4-[2-(chloromethyl)phenoxy]butyl}-4-methyl-1*H*-benzotriazol-5-yl)-3-{3-[(6-hydroxy-2,2-dioxo-2*H*-1,2λ<sup>6</sup>,3-benzoxathiazin-3(4*H*)-yl)methyl]-4-methoxyphenyl}propanoate (1 eq.) as a reactant, the title compound (white solid, 48% yield) was obtained.

**<sup>1</sup>H-NMR** (500 MHz, DMSO-d<sub>6</sub>) δ ppm: 7.67 (d, 1 H), 7.57 (d, 1 H), 7.44 (dd, 1 H), 7.34 (dd, 1 H), 7.29 (td, 1 H), 7.26 (d, 1 H), 7.01 (d, 1 H), 7 (dd, 1 H), 6.95 (t, 1 H), 6.87 (d, 1 H), 6.77 (d, 1 H), 6.64 (d, 1 H), 5.03 (s, 2 H), 4.81 (t, 1 H), 4.77 (t, 2 H), 4.41/4.34 (d+d, 2 H), 4.3/4.2 (d+d, 2 H), 4.13/4.06 (m+m, 2 H), 3.91 (qd, 2 H), 3.73 (s, 3 H), 3.2/3.15 (dd+dd, 2 H), 2.8 (s, 3 H), 2.21/2.02 (m+m, 2 H), 1.84 (m, 2 H), 1 (t, 3 H)

**STEP 5 : Preparation of EXAMPLE 53**

Using General Procedure 12 starting from ethyl [4-methoxy-39-methyl-35,35-dioxo-21,29,34-trioxa-35λ<sup>6</sup>-thia-1,14,15,16-tetraazaheptacyclo[28.5.3.1<sup>3,7</sup>.1<sup>9,13</sup>.0<sup>12,16</sup>.0<sup>22,27</sup>.0<sup>33,37</sup>]tetraconta-

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3(40),4,6,9(39),10,12,14,22,24,26,30,32,37-tridecaen-8-yl]acetate (1 eq.) as a reactant, the title compound (80% yield) was obtained.

The enantiopure products were obtained by chromatographic separation on chiral column.

#### 5 **Example 53a (E1)**

**HRMS** calculated for  $C_{36}H_{36}N_4O_8S$ : 684.2254;  $[M+H]^+$  found: 685.2315 ( $\delta = -1.7$  ppm)

#### **Example 53b (E2)**

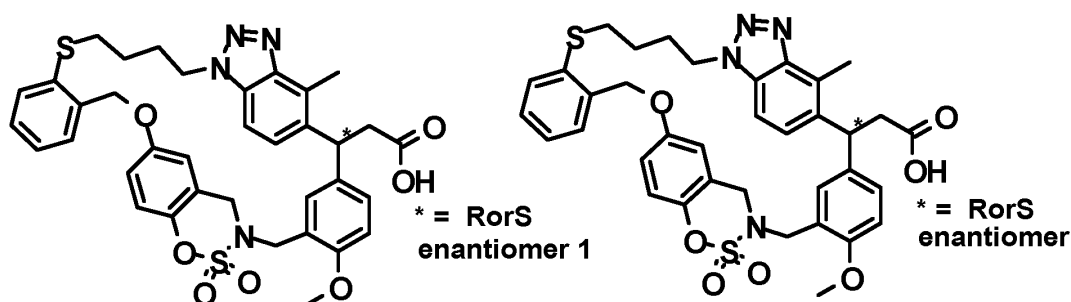
**HRMS** calculated for  $C_{36}H_{36}N_4O_8S$ : 684.2254;  $[M+H]^+$  found: 685.2317 ( $\delta = -1.4$  ppm)

10  **$^1H$ -NMR** (500 MHz, DMSO- $d_6$ )  $\delta$  ppm: 7.67 (d, 1 H), 7.55 (d, 1 H), 7.34 (dd, 1 H), 7.29 (t, 1 H), 7.23 (d, 1 H), 7.14 (d, 1 H), 7.01 (d, 1 H), 7 (dd, 1 H), 6.95 (t, 1 H), 6.88 (d, 1 H), 6.78 (d, 1 H), 6.63 (d, 1 H), 5.03 (s, 2 H), 4.79 (t, 1 H), 4.77 (t, 2 H), 4.4/4.33 (d+d, 2 H), 4.3/4.2 (d+d, 2 H), 4.14/4.06 (m+m, 2 H), 3.73 (s, 3 H), 3.09/3.05 (dd+dd, 2 H), 2.8 (s, 3 H), 2.21/2.03 (m+m, 2 H), 1.84 (qn, 2 H)

15  **$^{13}C$ -NMR** (125 MHz, DMSO- $d_6$ )  $\delta$  ppm: 173.2, 156.4, 156.3, 155.6, 146.4, 144.6, 137.7, 136.1, 131.5, 130.1, 129.7, 129.3, 129.1, 127, 126.6, 124.8, 121.9, 120.7, 119, 118.2, 116.3, 112.9, 111.9, 111.5, 108.2, 67.5, 65.1, 56.1, 49.8, 48.5, 48.1, 40.8, 40.4, 27.1, 26.4, 13.3

#### **EXAMPLE 54 :** [4-Methoxy-39-methyl-35,35-dioxo-29,34-dioxa-21,35 $\lambda^6$ -dithia-

20 1,14,15,16-tetraazaheptacyclo[28.5.3.1<sup>3,7</sup>.1<sup>9,13</sup>.0<sup>12,16</sup>.0<sup>22,27</sup>.0<sup>33,37</sup>]tetraconta-3(40),4,6,9(39),10,12,14,22,24,26,30,32,37-tridecaen-8-yl]acetic acid



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**STEP 1 : Preparation of ethyl 3-{3-[(6-hydroxy-2,2-dioxo-2*H*-1,2λ<sup>6</sup>,3-benzoxathiazin-3(4*H*)-yl)methyl]-4-methoxyphenyl}-3-[1-(4-{[2-(hydroxymethyl)phenyl]sulfanyl}butyl)-4-methyl-1*H*-benzotriazol-5-yl]propanoate**

5

Ethyl 3-[1-(4-chlorobutyl)-4-methyl-1*H*-benzotriazol-5-yl]-3-{3-[(6-hydroxy-2,2-dioxo-2*H*-1,2λ<sup>6</sup>,3-benzoxathiazin-3(4*H*)-yl)methyl]-4-methoxyphenyl}propanoate (1 eq., 1 g, 1.55 mmol) and (2-sulfanylphenyl)methanol (1.2 eq., 262 mg, 1.87 mmol) were dissolved in DMF (5 mL) and K<sub>2</sub>CO<sub>3</sub> (2 eq., 430 mg, 3.11 mmol) was added. The reaction mixture was stirred at RT for 10 2 h. After completion of the reaction, the mixture was poured into 10 ml of water and extracted with 2x30 ml of DCM. The organic layer was separated and dried over MgSO<sub>4</sub>. After filtration the mother liquor was evaporated to dryness to give a yellow crystalline product (1.15 g, 99% yield).

<sup>1</sup>H-NMR (500 MHz, DMSO-d<sub>6</sub>) δ ppm: 7.63 (d, 1 H), 7.5 (d, 1 H), 7.41 (dm, 1 H), 7.27 (d, 1 H), 7.23 (dd, 1 H), 7.22 (d, 1 H), 7.15 (td, 1 H), 7.12 (td, 1 H), 6.89 (d, 1 H), 6.84 (d, 1 H), 6.7 (dd, 1 H), 6.58 (d, 1 H), 4.82 (t, 1 H), 4.67 (t, 2 H), 4.48 (s, 2 H), 4.48 (s, 2 H), 4.21/4.17 (d+d, 2 H), 3.93 (q, 2 H), 3.69 (s, 3 H), 3.15 (d, 2 H), 2.94 (t, 2 H), 2.75 (s, 3 H), 2.01/1.51 (m+m, 4 H), 1 (t, 3 H)

**STEP 2 : Preparation of ethyl 3-[1-(4-{[2-(chloromethyl)phenyl]sulfanyl}butyl)-4-methyl-1*H*-benzotriazol-5-yl]-3-{3-[(6-hydroxy-2,2-dioxo-2*H*-1,2λ<sup>6</sup>,3-benzoxathiazin-3(4*H*)-yl)methyl]-4-methoxyphenyl}propanoate**

Using General Procedure 10 starting from ethyl 3-{3-[(6-hydroxy-2,2-dioxo-2*H*-1,2λ<sup>6</sup>,3-benzoxathiazin-3(4*H*)-yl)methyl]-4-methoxyphenyl}-3-[1-(4-{[2-(hydroxymethyl)phenyl]sulfanyl}butyl)-4-methyl-1*H*-benzotriazol-5-yl]propanoate (1 eq.) as a reactant, the title compound (98% yield) was obtained.

<sup>1</sup>H-NMR (500 MHz, DMSO-d<sub>6</sub>) δ ppm: 7.62 (d, 1 H), 7.5 (d, 1 H), 7.39 (dd, 1 H), 7.34 (dd, 1 H), 7.27 (d, 1 H), 7.24 (td, 1 H), 7.23 (dd, 1 H), 7.16 (td, 1 H), 6.89 (d, 1 H), 6.84 (d, 1 H), 6.71 (dd, 1 H), 6.59 (d, 1 H), 4.82 (t, 1 H), 4.74/4.7 (d+d, 2 H), 4.67 (t, 2 H), 4.48 (s, 2 H), 4.21/4.17



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(d+d, 2 H), 3.93 (q, 2 H), 3.69 (s, 3 H), 3.15 (d, 2 H), 3 (t, 2 H), 2.75 (s, 3 H), 2.01/1.51 (m+m, 4 H), 1 (t, 3 H)

**STEP 3 : Preparation of ethyl [4-methoxy-39-methyl-35,35-dioxo-29,34-dioxa-21,35 $\lambda^6$ -dithia-1,14,15,16-tetraazaheptacyclo[28.5.3.1<sup>3,7</sup>.1<sup>9,13</sup>.0<sup>12,16</sup>.0<sup>22,27</sup>.0<sup>33,37</sup>]tetraconta-3(40),4,6,9(39),10,12,14,22,24,26,30,32,37-tridecaen-8-yl]acetate**

Using General Procedure 11 starting from ethyl 3-[1-(4-{[2-(chloromethyl)phenyl]sulfanyl}butyl)-4-methyl-1*H*-benzotriazol-5-yl]-3-{3-[(6-hydroxy-2,2-dioxo-2*H*-1,2 $\lambda^6$ ,3-benzoxathiazin-3(4*H*)-yl)methyl]-4-methoxyphenyl}propanoate (1 eq.) as a reactant, the title compound (yellow crystals, 21% yield) was obtained.

The enantiopure final intermediates were obtained by chromatographic separation on chiral column.

**<sup>1</sup>H-NMR** (500 MHz, DMSO-d<sub>6</sub>)  $\delta$  ppm: 7.58 (d, 1 H), 7.53 (d, 1 H), 7.51 (d, 1 H), 7.38 (t, 1 H), 7.34 (d, 1 H), 7.34 (dd, 1 H), 7.31 (d, 1 H), 7.24 (t, 1 H), 6.86 (d, 1 H), 6.79 (dd, 1 H), 6.74 (d, 1 H), 6.72 (d, 1 H), 4.99/4.92 (d+d, 2 H), 4.82 (t, 1 H), 4.65 (t, 2 H), 4.47/4.4 (d+d, 2 H), 4.34/4.26 (d+d, 2 H), 3.9 (qd, 2 H), 3.72 (s, 3 H), 3.16/3.07 (m+m, 2 H), 3.14 (m, 2 H), 2.81 (s, 3 H), 2.04/1.9 (m+m, 2 H), 1.62 (m, 2 H), 0.99 (t, 3 H)

#### STEP 4 : Preparation of EXAMPLE 54

Using General Procedure 12 starting from ethyl [4-methoxy-39-methyl-35,35-dioxo-29,34-dioxa-21,35 $\lambda^6$ -dithia-1,14,15,16-tetraazaheptacyclo[28.5.3.1<sup>3,7</sup>.1<sup>9,13</sup>.0<sup>12,16</sup>.0<sup>22,27</sup>.0<sup>33,37</sup>]tetraconta-3(40),4,6,9(39),10,12,14,22,24,26,30,32,37-tridecaen-8-yl]acetate E1 (1 eq.) or E2 (1 eq.) as reactants, the title compounds (18% - 73% yields respectively) were obtained.

#### Example 54a (E1)

**HRMS** calculated for C<sub>36</sub>H<sub>36</sub>N<sub>4</sub>O<sub>7</sub>S<sub>2</sub> : 700.2025; [M+H]<sup>+</sup> found: 701.2100 ( $\delta$  = 0.3 ppm)

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**Example 54b (E2)**

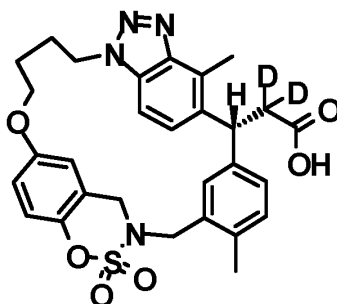
**HRMS** calculated for  $C_{36}H_{36}N_4O_7S_2$ : 700.2025;  $[M+H]^+$  found: 701.2101 ( $\delta = 0.4$  ppm)

**$^1H$ -NMR** (500 MHz, DMSO- $d_6$ )  $\delta$  ppm: 7.57 (d, 1 H), 7.53-7.21 (m, 4 H), 7.49 (d, 1 H), 7.33 (dd, 1 H), 7.26 (d, 1 H), 6.85 (d, 1 H), 6.79 (dd, 1 H), 6.76 (d, 1 H), 6.71 (d, 1 H), 4.98/4.91 (d+d, 2 H), 4.81 (t, 1 H), 4.64 (t, 2 H), 4.46/4.39 (d+d, 2 H), 4.33/4.26 (d+d, 2 H), 3.72 (s, 3 H), 3.16/3.06 (m+m, 2 H), 2.97 (d, 2 H), 2.8 (s, 3 H), 2.04/1.9 (m+m, 2 H), 1.61 (m, 2 H)

**$^{13}C$ -NMR** (125 MHz, DMSO- $d_6$ )  $\delta$  ppm: 130.3, 129.5, 127.2, 119, 116.4, 112.7, 111.4, 107.9, 68.4, 56, 49.9, 48.6, 47.4, 41.4, 41.1, 32.4, 28.5, 25.1, 13.4

10

**EXAMPLE 55a**: [(8*R*)-4,31-Dimethyl-27,27-dioxo-21,26-dioxa-27 $\lambda^6$ -thia-1,14,15,16-tetraazahexacyclo[20.5.3.1<sup>3,7</sup>.1<sup>9,13</sup>.0<sup>12,16</sup>.0<sup>25,29</sup>]dotriaconta-3(32),4,6,9(31),10,12,14,22,24,29-decaen-8-yl]( $^2H_2$ )acetic acid



15

To a stirred solution of ethyl [(8*R*)-4,31-dimethyl-27,27-dioxo-21,26-dioxa-27 $\lambda^6$ -thia-1,14,15,16-tetraazahexacyclo[20.5.3.1<sup>3,7</sup>.1<sup>9,13</sup>.0<sup>12,16</sup>.0<sup>25,29</sup>]dotriaconta-3(32),4,6,9(31),10,12,14,22,24,29-decaen-8-yl]acetate (1 eq., 100 mg, 0.1693 mmol) in methanol- $d_4$  (tetra-deutero-methanol, ( $^2H_3$ )methan( $^2H$ )ol) (2 mL) NaH (60% in mineral oil, 10 eq., 68 mg, 1.6936 mmol) was added slowly at RT. After the mixture was stirred for 5 min, the reaction vessel was closed and the mixture was stirred at 65 °C for 18 h. The reaction mixture was neutralised with 2 ml 1M aq. HCl solution, the white precipitate was filtered off, washed with 2x 5 ml water, dried in vacuo. The crude product was purified by reversed-phase

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chromatography using aq. 5 mM HCOOH solution-MeCN as an eluent to give the title compound (beige solid, 82 mg, 86% yield).

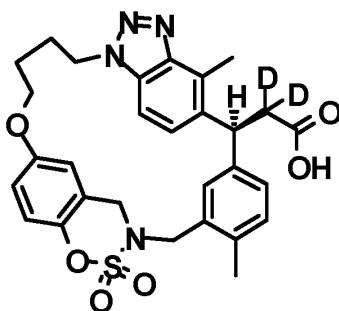
**HRMS** calculated for  $C_{29}D_2H_{28}N_4O_6S$ : 564.2012;  $[M+H]^+$  found: 565.2086 ( $\delta = 0.3$  ppm)

**$^1H$ -NMR** (500 MHz, DMSO- $d_6$ )  $\delta$  ppm: 12.19 (br., 1 H), 7.68 (d, 1 H), 7.49 (dd, 1 H), 7.43 (d, 1 H), 7.29 (d, 1 H), 6.99 (d, 1 H), 6.79 (dd, 1 H), 6.54 (d, 1 H), 5.85 (d, 1 H), 4.77 (m, 2 H), 4.74 (s, 1 H), 4.13/3.94 (d+d, 2 H), 3.99/3.84 (d+d, 2 H), 3.64/3.42 (m+m, 2 H), 2.62 (s, 3 H), 2.32 (s, 3 H), 2.21/2.06 (m+m, 2 H), 1.82/1.62 (m+m, 2 H)

**$^{13}C$ -NMR** (125 MHz, DMSO- $d_6$ )  $\delta$  ppm: 173.3, 131.3, 131.3, 128.6, 127.3, 119.5, 117.5, 111.2, 108, 67.8, 51.9, 48.8, 48.2, 41.6, 40.1, 26.7, 25.5, 18.5, 13.4

10

**EXAMPLE 55b** : [(8*S*)-4,31-Dimethyl-27,27-dioxo-21,26-dioxa-27 $\lambda^6$ -thia-1,14,15,16-tetraazahexacyclo[20.5.3.1<sup>3,7</sup>.1<sup>9,13</sup>.0<sup>12,16</sup>.0<sup>25,29</sup>]dotriaconta-3(32),4,6,9(31),10,12,14,22,24,29-decaen-8-yl]( $^2H_2$ )acetic acid



15

To a stirred solution of ethyl [(8*R*)-4,31-dimethyl-27,27-dioxo-21,26-dioxa-27 $\lambda^6$ -thia-1,14,15,16-tetraazahexacyclo[20.5.3.1<sup>3,7</sup>.1<sup>9,13</sup>.0<sup>12,16</sup>.0<sup>25,29</sup>]dotriaconta-3(32),4,6,9(31),10,12,14,22,24,29-decaen-8-yl]acetate (1eq., 200 mg, 0.338 mmol) in methanol- $d_4$  (tetradeutero-methanol, ( $^2H_3$ )methan( $^2H$ )ol) (4 mL) NaH (60% in mineral oil, 10 eq., 135 mg, 3.38 mmol) was added at RT slowly. After the mixture was stirred for 5 min, the reaction vessel was closed and the mixture was stirred at 65 °C overnight. The reaction mixture was neutralised with 2 ml 1M aq. HCl solution, the white precipitate was filtered off, washed with 2x 5 ml water, dried in vacuo. The crude product was purified by reversed-phase

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chromatography using aq. 5 mM HCOOH solution-MeCN as an eluent to give the title compound (white solid, 82 mg, 43% yield).

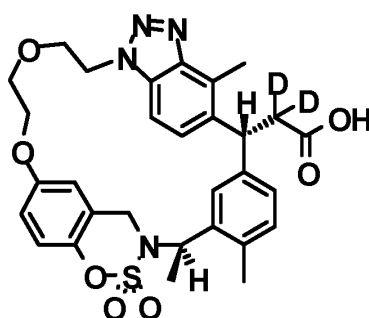
**HRMS** calculated for  $C_{29}D_{28}H_{28}N_4O_6S$ : 564.2012;  $[M+H]^+$  found: 565.2081 ( $\delta = -0.6$  ppm)

**$^1H$ -NMR** (500 MHz, DMSO- $d_6$ )  $\delta$  ppm: 12.19 (br., 1 H), 7.68 (d, 1 H), 7.49 (dd, 1 H), 7.43 (d, 1 H), 7.29 (d, 1 H), 6.99 (d, 1 H), 6.79 (dd, 1 H), 6.54 (d, 1 H), 5.85 (d, 1 H), 4.77 (m, 2 H), 4.74 (s, 1 H), 4.13/3.94 (d+d, 2 H), 3.99/3.84 (d+d, 2 H), 3.64/3.42 (m+m, 2 H), 2.62 (s, 3 H), 2.32 (s, 3 H), 2.21/2.06 (m+m, 2 H), 1.82/1.62 (m+m, 2 H)

**$^{13}C$ -NMR** (125 MHz, DMSO- $d_6$ )  $\delta$  ppm: 173.3, 131.3, 131.3, 128.6, 127.3, 119.5, 117.5, 111.2, 108, 67.8, 51.9, 48.8, 48.2, 41.6, 40.1, 26.7, 25.5, 18.5, 13.4

10

**EXAMPLE 56** : [(2*R*,8*R*)-2,4,32-Trimethyl-28,28-dioxo-19,22,27-trioxa-28 $\lambda^6$ -thia-1,14,15,16-tetraazahexacyclo[21.5.3.1<sup>3,7</sup>.1<sup>9,13</sup>.0<sup>12,16</sup>.0<sup>26,30</sup>]tritiaconta-3(33),4,6,9(32),10,12,14,23,25,30-decaen-8-yl]( $^2H_2$ )acetic acid



15

To a stirred solution of ethyl [(2*R*,8*R*)-2,4,32-trimethyl-28,28-dioxo-19,22,27-trioxa-28 $\lambda^6$ -thia-1,14,15,16-tetraazahexacyclo[21.5.3.1<sup>3,7</sup>.1<sup>9,13</sup>.0<sup>12,16</sup>.0<sup>26,30</sup>]tritiaconta-3(33),4,6,9(32),10,12,14,23,25,30-decaen-8-yl]acetate (1 eq., 150 mg, 0.2417 mmol) in methanol- $d_4$  (tetradeutero-methanol, ( $^2H_3$ )methan( $^2H$ )ol) (3 mL) NaH (60% in mineral oil, 10 eq., 97 mg, 2.417 mmol) was added slowly at RT. After the mixture was stirred for 5 min, the reaction vessel was closed and the mixture was stirred at 65 °C for 18h. The reaction mixture was neutralized with 2.5 ml 1M aq. HCl solution, the white precipitate was filtered off, washed with 2x5 ml water, dried in vacuo. The crude product was purified by reversed-phase

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chromatography using aq. 5 mM HCOOH solution-MeCN as an eluent to give the title compound (beige solid, 82 mg, 86%)

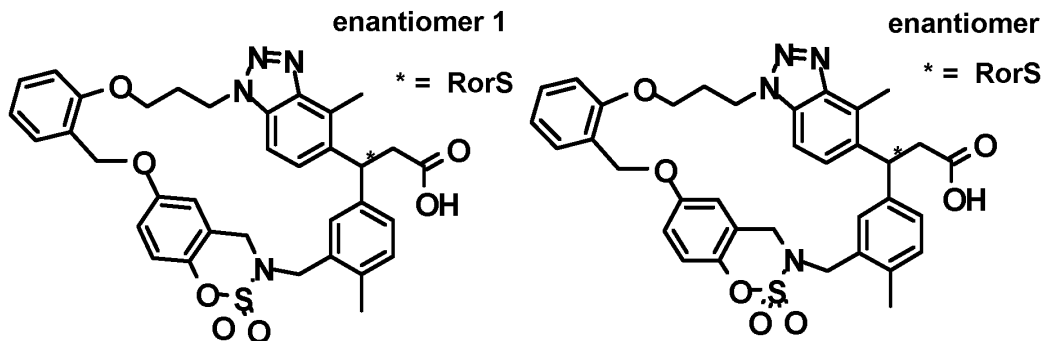
**HRMS** calculated for  $C_{30}D_2H_{30}N_4O_7S$ : 594.2117;  $[M+H]^+$  found: 595.2192 ( $\delta = 0.3$  ppm)

**$^1H$ -NMR** (500 MHz, DMSO- $d_6$ )  $\delta$  ppm: 12.23 (brs, 1 H), 7.65 (d, 1 H), 7.46 (dd, 1 H), 7.29 (d, 1 H), 7.12 (d, 1 H), 6.94 (d, 1 H), 6.9 (d, 1 H), 6.8 (dd, 1 H), 6.01 (d, 1 H), 5.25 (q, 1 H), 4.9 (s, 1 H), 4.82 (t, 2 H), 4.15/3.79 (d+d, 2 H), 4.11/4.03 (dt+dt, 2 H), 3.95/3.8 (m+m, 2 H), 3.7/3.68 (m+m, 2 H), 2.79 (s, 3 H), 2.33 (s, 3 H), 1.16 (d, 3 H)

**$^{13}C$ -NMR** (125 MHz, DMSO- $d_6$ )  $\delta$  ppm: 173.4, 155.5, 146.5, 145, 141.5, 137.7, 135.9, 135.5, 132.3, 131.6, 128.3, 127.9, 127, 126.6, 120, 119, 115.4, 114.1, 108.6, 69.3, 69.1, 68.5, 55.4, 48.8, 45.1, 41.1, 39.4, 18.6, 15.6, 13.4

**EXAMPLE 57** : [4,38-Dimethyl-34,34-dioxo-20,28,33-trioxa-34 $\lambda^6$ -thia-1,14,15,16-tetraazaheptacyclo[27.5.3.1<sup>3,7</sup>.1<sup>9,13</sup>.0<sup>12,16</sup>.0<sup>21,26</sup>.0<sup>32,36</sup>]nonatriaconta-3(39),4,6,9(38),10,12,14,21,23,25,29,31,36-tridecaen-8-yl]acetic acid

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#### STEP A1 : Preparation of 3-(4-bromo-3-methyl-2-nitroanilino)propan-1-ol

1-Bromo-4-fluoro-2-methyl-3-nitrobenzene (1 eq., 90 g, 385 mmol) was taken up in 3-aminopropan-1-ol (2.2 eq, 64 g, 847 mmol) under  $N_2$  at RT. The mixture was heated at 80°C for 1 h. After completion of the reaction, the mixture was cooled to Rt and diluted with DCM. This solution was washed with water. The organic layer was dried over  $MgSO_4$ , filtered and

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evaporated to dryness to get the crude product, which was purified by trituration with petroleum ether (104 g, 94% yield).

**<sup>1</sup>H-NMR** (500 MHz, DMSO-d<sub>6</sub>) δ ppm: 7.54 (d, 1 H), 6.74 (d, 1 H), 6.24 (t, 1 H), 4.61 (t, 1 H), 3.47 (q, 2 H), 3.19 (q, 2 H), 2.25 (s, 3 H), 1.67 (m, 2 H)

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#### **STEP A2 : Preparation of 3-(2-amino-4-bromo-3-methylanilino)propan-1-ol**

To the stirred solution of 3-(4-bromo-3-methyl-2-nitroanilino)propan-1-ol (1 eq., 104 g, 360 mmol) in EtOH (1000 mL) and water (200 mL), NH<sub>4</sub>Cl (5 eq., 97.2 g, 1800 mmol) and iron powder (5 eq., 100.8 g, 1800 mmol) were added and the mixture was heated at 90°C overnight. After completion of the reaction, the mixture was cooled to RT and filtered through a Celite pad. The filtrate was evaporated till water and extracted with EtOAc. The organic layer was separated and dried over Na<sub>2</sub>SO<sub>4</sub>. Filtration and evaporation of the mother liquor gave the crude product, which was purified by normal phase silica gel chromatography using EtOAc-petroleum ether (0:100 to 50:50%) as an eluent (80 g, 86% yield).

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**<sup>1</sup>H-NMR** (500 MHz, DMSO-d<sub>6</sub>) δ ppm: 6.71 (d, 1 H), 6.26 (d, 1 H), 4.58 (br, 3 H), 4.48 (br, 1 H), 3.52 (q, 2 H), 3.04 (q, 2 H), 2.16 (s, 3 H), 1.73 (m, 2 H)

#### **STEP A3 : Preparation 3-(5-bromo-4-methyl-1H-benzotriazol-1-yl)propan-1-ol**

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To the stirred solution of 3-(2-amino-4-bromo-3-methylanilino)propan-1-ol (1 eq., 10 g, 0.038 mol) in THF (150 mL) and AcOH (15 mL), 3-methylbutyl nitrite (3 eq., 13.6 g, 0.115 mol) was added at RT. The reaction mixture was stirred for 1h at RT. After completion of the reaction, the mixture was poured into ice-water. Extraction with EtOAc, drying of the organic layer over MgSO<sub>4</sub>, filtration and evaporation to dryness afforded the crude product, which was purified by normal phase silica gel chromatography using EtOAc-petroleum ether (0:100 to 40:60%) to give the title compound (4 g, 38% yield).

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**<sup>1</sup>H-NMR** (500 MHz, DMSO-d<sub>6</sub>) δ ppm: 7.70 (d, 2 H), 7.68 (d, 2 H), 4.74 (t, 2 H), 4.67 (t, 1 H), 3.40 (q, 2 H), 2.72 (s, 3 H), 2.05 (m, 2 H)

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**STEP A4 : Preparation of ethyl (2E)-3-[1-(3-hydroxypropyl)-4-methyl-1H-benzotriazol-5-yl]prop-2-enoate**

To the stirred solution of 3-(5-bromo-4-methyl-1H-benzotriazol-1-yl)propan-1-ol (1 eq., 8 g, 0.029 mol) in a mixture of THF (120 mL) and water (20 mL) Na<sub>2</sub>CO<sub>3</sub> (2.5 eq., 7.85 g, 0.079 mol) and ethyl (2E)-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)prop-2-enoate (1.2 eq., 8.04 g, 0.035 mol) were added and the mixture was degassed with N<sub>2</sub> for 30 min. Finally A<sup>la</sup>phos.PdCl<sub>2</sub> catalyst (0.02 eq., 0.52 g, 0.0007 mol) was added and the mixture was heated at 70°C for 2 h. After completion of the reaction the mixture was poured into ice-water and extracted with EtOAc. The organic phase was dried and evaporated. The received crude product was purified by trituration with Et<sub>2</sub>O to give the title compound (12.6 g, 47% yield).

<sup>1</sup>H-NMR (500 MHz, DMSO-d<sub>6</sub>) δ ppm: 8.03 (d, 1 H), 7.98 (d, 1 H), 7.71 (d, 1 H), 6.66 (d, 1 H), 4.75 (t, 2 H), 4.68 (t, 1 H), 4.22 (q, 2 H), 3.39 (q, 2 H), 2.81 (s, 3 H), 2.04 (m, 2 H), 1.28 (t, 3H)

**STEP 1 : Preparation of ethyl 3-(3-{[6-(benzyloxy)-2,2-dioxo-2H-1,2λ<sup>6</sup>,3-benzoxathiazin-3(4H)-yl]methyl}-4-methylphenyl)-3-[1-(3-hydroxypropyl)-4-methyl-1H-benzotriazol-5-yl]propanoate**

Using General Procedure 6 starting from ethyl (2E)-3-[1-(3-hydroxypropyl)-4-methyl-1H-benzotriazol-5-yl]prop-2-enoate (1 eq.) and 6-(benzyloxy)-3-{[2-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]methyl}-3,4-dihydro-2H-1,2λ<sup>6</sup>,3-benzoxathiazine-2,2-dione (2 eq.) as reactants, the title compound (yellow solid foam, 77% yield) was obtained.

<sup>1</sup>H-NMR (500 MHz, DMSO-d<sub>6</sub>) δ ppm: 7.58 (d, 1 H), 7.49-7.31 (m, 5 H), 7.49 (d, 1 H), 7.23 (d, 1 H), 7.19 (dd, 1 H), 7.13 (d, 1 H), 7.13 (d, 1 H), 7.07 (dd, 1 H), 6.97 (d, 1 H), 5.11 (s, 2 H), 4.85 (t, 1 H), 4.65 (t, 2 H), 4.65 (t, 1 H), 4.44 (s, 2 H), 4.22 (s, 2 H), 3.92 (q, 2 H), 3.36 (m, 2 H), 3.19/3.15 (dd+dd, 2 H), 2.77 (s, 3 H), 2.21 (s, 3 H), 1.99 (m, 2 H), 0.99 (t, 3 H)

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**STEP 2 : Preparation of ethyl 3-{3-[(6-hydroxy-2,2-dioxo-2*H*-1,2λ<sup>6</sup>,3-benzoxathiazin-3(4*H*)-yl)methyl]-4-methylphenyl}-3-[1-(3-hydroxypropyl)-4-methyl-1*H*-benzotriazol-5-yl]propanoate**

5 Using General Procedure 8 starting from ethyl 3-{3-[(6-(benzyloxy)-2,2-dioxo-2*H*-1,2λ<sup>6</sup>,3-benzoxathiazin-3(4*H*)-yl)methyl]-4-methylphenyl}-3-[1-(3-hydroxypropyl)-4-methyl-1*H*-benzotriazol-5-yl]propanoate (1 eq.) as a reactant, the title compound (white solid foam, 93% yield) was obtained.

<sup>1</sup>H-NMR (500 MHz, DMSO-d<sub>6</sub>) δ ppm: 9.71 (brs., 1 H), 7.6 (d, 1 H), 7.5 (d, 1 H), 7.22 (d, 1  
10 H), 7.19 (dd, 1 H), 7.13 (d, 1 H), 6.99 (d, 1 H), 6.79 (dd, 1 H), 6.6 (d, 1 H), 4.84 (t, 1 H), 4.68 (t, 2 H), 4.67 (br., 1 H), 4.4/4.36 (d+d, 2 H), 4.21/4.17 (d+d, 2 H), 3.94 (q, 2 H), 3.38 (t, 2 H), 3.19/3.15 (dd+dd, 2 H), 2.76 (s, 3 H), 2.22 (s, 3 H), 2.01 (m, 2 H), 1 (t, 3 H)

**STEP 3 : Preparation of ethyl 3-[1-(3-chloropropyl)-4-methyl-1*H*-benzotriazol-5-yl]-3-{3-[(6-hydroxy-2,2-dioxo-2*H*-1,2λ<sup>6</sup>,3-benzoxathiazin-3(4*H*)-yl)methyl]-4-methylphenyl}propanoate**

Using General Procedure 10 starting from ethyl 3-{3-[(6-hydroxy-2,2-dioxo-2*H*-1,2λ<sup>6</sup>,3-benzoxathiazin-3(4*H*)-yl)methyl]-4-methylphenyl}-3-[1-(3-hydroxypropyl)-4-methyl-1*H*-  
20 benzotriazol-5-yl]propanoate (1 eq.) as a reactant, the title compound (yellow solid foam, 97% yield) was obtained.

<sup>1</sup>H-NMR (500 MHz, DMSO-d<sub>6</sub>) δ ppm: 9.72 (brs., 1 H), 7.62 (d, 1 H), 7.53 (d, 1 H), 7.22 (d, 1 H), 7.2 (dd, 1 H), 7.13 (d, 1 H), 6.99 (d, 1 H), 6.79 (dd, 1 H), 6.6 (d, 1 H), 4.84 (t, 1 H), 4.77 (t, 2 H), 4.39/4.35 (d+d, 2 H), 4.21/4.17 (d+d, 2 H), 3.94 (q, 2 H), 3.61 (m, 2 H), 3.19/3.15  
25 (dd+dd, 2 H), 2.76 (s, 3 H), 2.34 (m, 2 H), 2.22 (s, 3 H), 1 (t, 3 H)

**STEP 4 : Preparation of ethyl 3-{1-[3-(2-formylphenoxy)propyl]-4-methyl-1*H*-benzotriazol-5-yl}-3-{3-[(6-hydroxy-2,2-dioxo-2*H*-1,2λ<sup>6</sup>,3-benzoxathiazin-3(4*H*)-yl)methyl]-4-methylphenyl}propanoate**



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Ethyl 3-[1-(3-chloropropyl)-4-methyl-1*H*-benzotriazol-5-yl]-3-{3-[(6-hydroxy-2,2-dioxo-2*H*-1,2λ<sup>6</sup>,3-benzoxathiazin-3(4*H*)-yl)methyl]-4-methylphenyl}propanoate (1 eq., 0.65 g, 1.1 mmol) was dissolved in dry N,N-dimethylacetamide (5 mL) and 2-hydroxybenzaldehyde (34 eq., 4 mL, 37.536 mmol) was added followed by addition of Cs<sub>2</sub>CO<sub>3</sub> (5.55 eq., 2.0 g, 6.1 mmol). The solution was heated at 120° for 2h. The crude product was purified by normal phase silica gel chromatography using DCM-MeOH (100:0 to 95:5) as eluents resulted in 0.49 g (66% yield) of the title compound as a light orange solid.

<sup>1</sup>H-NMR (500 MHz, DMSO-d<sub>6</sub>) δ ppm: 10.12 (d, 1 H), 9.7 (brs, 1 H), 7.63 (d, 1 H), 7.62 (d, 1 H), 7.58 (t, 1 H), 7.45 (d, 1 H), 7.2 (d, 1 H), 7.16 (dd, 1 H), 7.12 (d, 1 H), 7.1 (d, 1 H), 7.03 (t, 1 H), 6.99 (d, 1 H), 6.78 (dd, 1 H), 6.6 (d, 1 H), 4.89 (t, 2 H), 4.82 (t, 1 H), 4.39/4.35 (d+d, 2 H), 4.21/4.16 (d+d, 2 H), 4.11 (t, 2 H), 3.93 (q, 2 H), 3.17/3.11 (dd+dd, 2 H), 2.73 (s, 3 H), 2.41 (qn, 2 H), 2.22 (s, 3 H), 1 (t, 3 H)

**STEP 5: Preparation of ethyl 3-{3-[(6-hydroxy-2,2-dioxo-2*H*-1,2λ<sup>6</sup>,3-benzoxathiazin-3(4*H*)-yl)methyl]-4-methylphenyl}-3-(1-{3-[2-(hydroxymethyl)phenoxy]propyl}-4-methyl-1*H*-benzotriazol-5-yl)propanoate**

Ethyl 3-{1-[3-(2-formylphenoxy)propyl]-4-methyl-1*H*-benzotriazol-5-yl}-3-{3-[(6-hydroxy-2,2-dioxo-2*H*-1,2λ<sup>6</sup>,3-benzoxathiazin-3(4*H*)-yl)methyl]-4-methylphenyl}propanoate (1 eq., 0.48 g, 0.69 mmol) was dissolved in dry EtOH (5 mL), and sodium borohydride (3.77 eq., 0.10 g, 2.6 mmol) was added. The solution was stirred at RT for 2h. The reaction mixture was poured on crushed ice and concentrated. The residue was partitioned between water and EtOAc, the phases were separated and the aq. phase was extracted with additional portions of EtOAc. The collected organic phases were dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and evaporated. Drying of the residue in high vacuo at RT resulted in 0.466 g (97% yield) of a title compound as an off-white foamy material.

<sup>1</sup>H-NMR (500 MHz, DMSO-d<sub>6</sub>) δ ppm: 9.56 (brs, 1 H), 7.61 (d, 1 H), 7.48 (d, 1 H), 7.36 (d, 1 H), 7.2 (d, 1 H), 7.17 (dd, 1 H), 7.14 (t, 1 H), 7.13 (d, 1 H), 6.96 (d, 1 H), 6.91 (t, 1 H), 6.82 (d, 1 H), 6.76 (dd, 1 H), 6.56 (d, 1 H), 4.84 (t, 1 H), 4.83 (t, 2 H), 4.52 (s, 2 H), 4.35 (s, 2 H),

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4.2/4.16 (d+d, 2 H), 3.94 (m, 2 H), 3.93 (q, 2 H), 3.17/3.13 (dd+dd, 2 H), 2.75 (s, 3 H), 2.33 (qn, 2 H), 2.22 (s, 3 H), 1 (t, 3 H)

**STEP 6 : Preparation of ethyl [4,38-dimethyl-34,34-dioxo-20,28,33-trioxa-34 $\lambda^6$ -thia-1,14,15,16-tetraazaheptacyclo[27.5.3.1<sup>3,7</sup>.1<sup>9,13</sup>.0<sup>12,16</sup>.0<sup>21,26</sup>.0<sup>32,36</sup>]nonatriaconta-3(39),4,6,9(38),10,12,14,21,23,25,29,31,36-tridecaen-8-yl]acetate**

Ethyl 3-{3-[(6-hydroxy-2,2-dioxo-2*H*-1,2 $\lambda^6$ ,3-benzoxathiazin-3(4*H*)-yl)methyl]-4-methylphenyl}-3-(1-{3-[2-(hydroxymethyl)phenoxy]propyl}-4-methyl-1*H*-benzotriazol-5-yl)propanoate (1 eq., 0.66 mmol, 0.46 g) was dissolved in dry THF (40 mL) and PPh<sub>3</sub> (3 eq., 0.52 g, 2 mmol) was added followed by addition of DIAD (3 eq., 0.40 g, 2.0 mmol) while cooling. The reaction mixture was stirred at RT for 1.5h. The solvent was evaporated and the crude product was purified by normal phase silica gel chromatography using heptane-EtOAc (100:0 to 30:70) as eluents resulted in 0.187 g (42% yield) of the title compound as a white foamy material.

The enantiopure final intermediates were obtained by chromatographic separation on chiral column. (ee~99.9%)

**<sup>1</sup>H-NMR** (500 MHz, DMSO-d<sub>6</sub>)  $\delta$  ppm: 7.63 (d, 1 H), 7.58 (d, 1 H), 7.58 (dm, 1 H), 7.36 (dd, 1 H), 7.35 (d, 1 H), 7.33 (m, 1 H), 7.22 (dd, 1 H), 7.17 (d, 1 H), 7.15 (d, 1 H), 7.06 (dm, 1 H), 7.02 (m, 1 H), 6.91 (d, 1 H), 5.27 (s, 2 H), 4.9/4.82 (m+m, 2 H), 4.85 (t, 1 H), 4.43/4.09 (d+d, 2 H), 4.29/4.02 (d+d, 2 H), 4.18/4.02 (m+m, 2 H), 3.88 (m, 2 H), 3.19/3.11 (dd+dd, 2 H), 2.81 (s, 3 H), 2.37/2.27 (m+m, 2 H), 2.28 (s, 3 H), 0.96 (t, 3 H)

**STEP 7 : Preparation of EXAMPLE 57**

Using General Procedure 12 starting from ethyl [4,38-dimethyl-34,34-dioxo-20,28,33-trioxa-34 $\lambda^6$ -thia-1,14,15,16-tetraazaheptacyclo[27.5.3.1<sup>3,7</sup>.1<sup>9,13</sup>.0<sup>12,16</sup>.0<sup>21,26</sup>.0<sup>32,36</sup>]nonatriaconta-3(39),4,6,9(38),10,12,14,21,23,25,29,31,36-tridecaen-8-yl]acetate E1 (1 eq.) or E2 (1 eq.) as reactants, the title compounds (75% - 83% yields respectively) were obtained.

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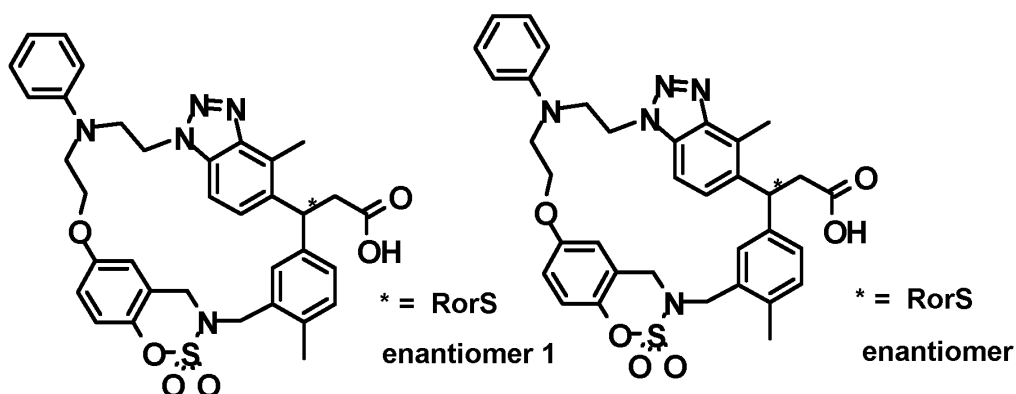
**Example 57a (E1)**HRMS calculated for  $C_{35}H_{34}N_4O_7S$ : 654.2148;  $[M+H]^+$  found: 655.2224 ( $\delta = 0.5$  ppm)**Example 57b (E2)**5 HRMS calculated for  $C_{35}H_{34}N_4O_7S$ : 654.2148;  $[M+H]^+$  found: 655.2231 ( $\delta = 1.5$  ppm)

$^1H$ -NMR (500 MHz, DMSO- $d_6$ )  $\delta$  ppm: 12.07 (brs, 1 H), 7.63 (d, 1 H), 7.58 (d, 1 H), 7.57 (s, 1 H), 7.36 (dd, 1 H), 7.34 (t, 1 H), 7.33 (d, 1 H), 7.21 (dd, 1 H), 7.16 (d, 1 H), 7.15 (d, 1 H), 7.07 (d, 1 H), 7.02 (t, 1 H), 6.91 (d, 1 H), 5.27 (s, 2 H), 4.9/4.82 (m+m, 2 H), 4.83 (t, 1 H), 4.43/4.1 (d+d, 2 H), 4.28/4.03 (d+d, 2 H), 4.17/4.05 (m+m, 2 H), 3.07/3.03 (dd+dd, 2 H), 2.81 (s, 3 H),  
 10 2.37/2.28 (m+m, 2 H), 2.28 (s, 3 H)

$^{13}C$ -NMR (125 MHz, DMSO- $d_6$ )  $\delta$  ppm: 173.2, 156.1, 156.1, 146.2, 144.8, 142.2, 137.4, 136.2, 132.4, 131.8, 131.2, 130.1, 129.9, 129.4, 129.3, 127.3, 126.8, 125, 120.9, 119.6, 118.3, 117, 112.4, 111.8, 107.7, 65.4, 64, 51.9, 49.1, 44.3, 41.1, 40.8, 30.1, 18.3, 13.3

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**EXAMPLE 58** : [4,32-Dimethyl-28,28-dioxo-19-phenyl-22,27-dioxa-28 $\lambda^6$ -thia-1,14,15,16,19-pentaazahexacyclo[21.5.3.1<sup>3,7</sup>.1<sup>9,13</sup>.0<sup>12,16</sup>.0<sup>26,30</sup>]tritiaconta-3(33),4,6,9(32),10,12,14,23,25,30-decaen-8-yl]acetic acid



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**STEP A1 : Preparation of 2-(4-bromo-3-methyl-2-nitroanilino)ethan-1-ol**

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1-Bromo-4-fluoro-2-methyl-3-nitrobenzene (1 eq., 600 g, 2.56 mol) was taken up in ethanolamine (2.5 eq, 332 g, 5.45 mol) under N<sub>2</sub> at RT. After heating at 95°C for 1.5 h, the reaction mixture was cooled to Rt and diluted with DCM. The solution was washed with water. The organic layer was dried over MgSO<sub>4</sub> and evaporated to dryness to get the crude product, which was purified by trituration with petroleum ether to give the title compound (630g, 89% yield).

<sup>1</sup>H-NMR (500 MHz, DMSO-d<sub>6</sub>) δ ppm: 7.59 (d, 1H), 6.79 (d, 1H), 6.09 (t, 1H), 4.84 (t, 1H), 3.54 (q, 2H), 3.19 (q, 2H), 2.27 (s, 3H)

#### 10 STEP A2 : Preparation of 2-(2-amino-4-bromo-3-methylanilino)ethan-1-ol

To the stirred solution of 2-(4-bromo-3-methyl-2-nitroanilino)ethan-1-ol (1 eq., 630 g, 2.29 mol) in EtOH (500 mL) and water (100 mL), NH<sub>4</sub>Cl (5 eq., 611 g, 11.45 mol) and zinc powder (5 eq., 744 g, 11.45 mol) were added and the mixture was heated at 95°C for 12h. After completion of the reaction, the mixture was filtered through a pad of Celite. The filtrate was evaporated and the residue was stirred for 3 h in 2 L water. The precipitated product was filtered off, dried and purified by trituration with pentane. (430 g, 77% yield)

<sup>1</sup>H-NMR (500 MHz, DMSO-d<sub>6</sub>) δ ppm: 6.72 (d, 1H), 6.28 (d, 1H), 4.67 (t, 1H), 4.58 (s, 2H), 4.51 (t, 1H), 3.59 (q, 2H), 3.06 (q, 2H), 2.17 (s, 3H)

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#### STEP A3 : Preparation of 2-(5-bromo-4-methyl-1H-benzotriazol-1-yl)ethan-1-ol

To the stirred solution of 2-(2-amino-4-bromo-3-methylanilino)ethan-1-ol (1 eq., 160 g, 0.652 mol) and tetrafluoroboric acid (2 eq., 160 mL, 1.3 mol) in MeCN (1500 mL), 3-methylbutyl nitrite (1.5 eq., 114.7 g, 0.979 mol) and tetrafluoroboric acid (2 eq., 160 mL, 1.3 mol) in MeCN were added within 2.5 h. The internal temperature must remain under 5°C during this process. After completion of the reaction, the mixture was poured into ice-water, basified with 10% NaOH solution and extracted with EtOAc. The organic layer was dried over MgSO<sub>4</sub> and evaporated to dryness. The crude product was purified by column chromatography (90 g, 48% yield).

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<sup>1</sup>H-NMR (500 MHz, DMSO-d<sub>6</sub>) δ ppm: 7.67 (s, 2 H), 4.98 (t, 1 H), 4.74 (t, 2 H), 3.86 (q, 2 H), 2.72 (s, 3 H)

**STEP A4 : Preparation of ethyl (2E)-3-[1-(2-hydroxyethyl)-4-methyl-1H-benzotriazol-5-yl]prop-2-enoate**

To the stirred solution of 2-(5-bromo-4-methyl-1H-benzotriazol-1-yl)ethan-1-ol (1 eq., 50 g, 0.19 mol) in a mixture of THF (450 mL) and water (50 mL), Na<sub>2</sub>CO<sub>3</sub> (2.5 eq., 51.2 g, 0.48 mol) and ethyl (2E)-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)prop-2-enoate (1.2 eq., 53 g, 0.23 mol) were added and the mixture was degassed with N<sub>2</sub> for 30 min. A<sup>1</sup>phos.PdCl<sub>2</sub> catalyst (0.02 eq., 2.76 g, 0.04 mol) was added and the mixture was heated at 70°C for 8 h. After completion of the reaction the mixture was poured into ice-water and extracted with EtOAc. The organic phase was dried and evaporated. The received crude product was purified by trituration with Et<sub>2</sub>O (46 g, 86% yield).

<sup>1</sup>H-NMR (500 MHz, DMSO-d<sub>6</sub>) δ ppm: 8.03 (d, 1 H), 7.95 (d, 1 H), 7.70 (d, 1 H), 6.65 (d, 1 H), 4.98 (t, 1 H), 4.74 (t, 2 H), 4.22 (q, 2 H), 3.87 (q, 2 H), 2.82 (s, 3 H), 1.28 (t, 3 H)

**STEP 1 : Preparation of ethyl 3-(3-{[6-(benzyloxy)-2,2-dioxo-2H-1,2λ<sup>6</sup>,3-benzoxathiazin-3(4H)-yl]methyl}-4-methylphenyl)-3-[1-(2-hydroxyethyl)-4-methyl-1H-benzotriazol-5-yl]propanoate**

Using General Procedure 6 starting from ethyl (2E)-3-[1-(2-hydroxyethyl)-4-methyl-1H-benzotriazol-5-yl]prop-2-enoate (1 eq.) and 6-(benzyloxy)-3-{[2-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]methyl}-3,4-dihydro-2H-1,2λ<sup>6</sup>,3-benzoxathiazine-2,2-dione (1.3 eq.) as reactants, the title compound (yellow solid foam, 82% yield) was obtained.

<sup>1</sup>H-NMR (500 MHz, DMSO-d<sub>6</sub>) δ ppm: 7.58 (d, 1 H), 7.47 (m, 2 H), 7.47 (d, 1 H), 7.41 (tm, 2 H), 7.35 (tm, 1 H), 7.24 (d, 1 H), 7.18 (dd, 1 H), 7.14 (d, 1 H), 7.13 (d, 1 H), 7.07 (dd, 1 H), 6.97 (d, 1 H), 5.11 (s, 2 H), 4.95 (t, 1 H), 4.85 (t, 1 H), 4.64 (t, 2 H), 4.46/4.42 (d+d, 2 H), 4.24/4.2

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(d+d, 2 H), 3.93 (q, 2 H), 3.81 (q, 2 H), 3.2/3.15 (dd+dd, 2 H), 2.77 (s, 3 H), 2.21 (s, 3 H), 1.01 (t, 3 H)

**STEP 2 : Preparation of ethyl 3-(3-{[6-(benzyloxy)-2,2-dioxo-2*H*-1,2λ<sup>6</sup>,3-benzoxathiazin-3(4*H*)-yl]methyl}-4-methylphenyl)-3-[1-(2-chloroethyl)-4-methyl-1*H*-benzotriazol-5-yl]propanoate**

Using General Procedure 10 starting from ethyl 3-(3-{[6-(benzyloxy)-2,2-dioxo-2*H*-1,2λ<sup>6</sup>,3-benzoxathiazin-3(4*H*)-yl]methyl}-4-methylphenyl)-3-[1-(2-hydroxyethyl)-4-methyl-1*H*-benzotriazol-5-yl]propanoate (1 eq.) as a reactant, the title compound (beige solid foam, 88% yield) was obtained. The product was used in the next step without further purification.

<sup>1</sup>H-NMR (500 MHz, DMSO-d<sub>6</sub>) δ ppm: 7.65 (d, 1 H), 7.52 (d, 1 H), 7.46 (d, 2 H), 7.44 (t, 2 H), 7.35 (t, 1 H), 7.25 (d, 1 H), 7.2 (dd, 1 H), 7.14 (d, 1 H), 7.14 (d, 1 H), 7.07 (dd, 1 H), 6.96 (d, 1 H), 5.1 (s, 2 H), 4.99 (t, 2 H), 4.85 (t, 1 H), 4.46/4.42 (d+d, 2 H), 4.23/4.2 (d+d, 2 H), 4.12 (t, 2 H), 3.93 (q, 2 H), 3.2/3.16 (dd+dd, 2 H), 2.78 (s, 3 H), 2.21 (s, 3 H), 0.98 (t, 3 H)

**STEP 3 : Preparation of ethyl 3-(3-{[6-(benzyloxy)-2,2-dioxo-2*H*-1,2λ<sup>6</sup>,3-benzoxathiazin-3(4*H*)-yl]methyl}-4-methylphenyl)-3-[1-{2-[(2-hydroxyethyl)(phenyl)amino]ethyl}-4-methyl-1*H*-benzotriazol-5-yl]propanoate**

Ethyl 3-(3-{[6-(benzyloxy)-2,2-dioxo-2*H*-1,2λ<sup>6</sup>,3-benzoxathiazin-3(4*H*)-yl]methyl}-4-methylphenyl)-3-[1-(2-chloroethyl)-4-methyl-1*H*-benzotriazol-5-yl]propanoate (1 eq., 1 g, 1.378 mmol) was dissolved in 2-anilinoethanol (20 eq., 3.78 g, 27.56 mmol). The reaction mixture was heated at 130 °C for 13 h. After cooling to Rt, the mixture was diluted with water and extracted with EtOAc. The organic phase was dried over MgSO<sub>4</sub>, filtered and concentrated to dryness to give the crude product, which was purified via normal phase silica gel chromatography using heptane-AcOEt (0 to 50:50) as an eluent to give the title compound (643 mg, white solid, 59% yield).

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<sup>1</sup>H-NMR (500 MHz, DMSO-d<sub>6</sub>) δ ppm: 7.48 (s, 1 H), 7.48 (s, 1 H), 7.48-7.31 (m, 5 H), 7.22 (d, 1 H), 7.17 (dd, 1 H), 7.15-6.55 (m, 5 H), 7.14 (d, 1 H), 7.14 (d, 1 H), 7.07 (dd, 1 H), 6.96 (d, 1 H), 5.1 (s, 2 H), 4.84 (t, 1 H), 4.78 (t, 2 H), 4.65 (t, 1 H), 4.46/4.42 (d+d, 2 H), 4.23/4.2 (d+d, 2 H), 3.92 (q, 2 H), 3.84 (m, 2 H), 3.36 (m, 2 H), 3.16 (m, 2 H), 3.09 (m, 2 H), 2.75 (s, 3 H),  
 5 2.21 (s, 3 H), 0.99 (t, 3 H)

**STEP 4: Preparation of ethyl 3-{3-[(6-hydroxy-2,2-dioxo-2*H*-1,2λ<sup>6</sup>,3-benzoxathiazin-3(4*H*)-yl)methyl]-4-methylphenyl}-3-(1-{2-[(2-hydroxyethyl)(phenyl)amino]ethyl}-4-methyl-1*H*-benzotriazol-5-yl)propanoate**  
 10

Ethyl 3-(3-{[6-(benzyloxy)-2,2-dioxo-2*H*-1,2λ<sup>6</sup>,3-benzoxathiazin-3(4*H*)-yl)methyl]-4-methylphenyl}-3-(1-{2-[(2-hydroxyethyl)(phenyl)amino]ethyl}-4-methyl-1*H*-benzotriazol-5-yl)propanoate (1 eq., 637 mg, 0.806 mmol) and Pd/C catalyst (230 mg) were suspended in EtOH  
 15 (25 mL) and dioxane (5 mL). The mixture was hydrogenated in a stainless steel reaction vessel under 2 bar pressure at RT for 18 hours. Filtration through a Celite pad and evaporation to dryness resulted in the crude product, which was triturated with Et<sub>2</sub>O then dissolved in EtOH and evaporated to give the title compound (530 mg, white solid, 94% yield).

<sup>1</sup>H-NMR (500 MHz, DMSO-d<sub>6</sub>) δ ppm: 9.7 (s, 1 H), 7.6 (d, 1 H), 7.5 (d, 1 H), 7.21 (d, 1 H),  
 20 7.17 (dd, 1 H), 7.13-6.59 (m, 5 H), 7.13 (d, 1 H), 6.99 (d, 1 H), 6.79 (dd, 1 H), 6.61 (d, 1 H), 4.83 (t, 1 H), 4.81 (t, 2 H), 4.66 (t, 1 H), 4.4/4.36 (d+d, 2 H), 4.21/4.17 (d+d, 2 H), 3.93 (q, 2 H), 3.85 (m, 2 H), 3.38 (q, 2 H), 3.17 (d, 2 H), 3.11 (t, 2 H), 2.74 (s, 3 H), 2.22 (s, 3 H), 1 (t, 3 H)

**STEP 5: Preparation of ethyl [4,32-dimethyl-28,28-dioxo-19-phenyl-22,27-dioxa-28λ<sup>6</sup>-thia-1,14,15,16,19-pentaazahexacyclo[21.5.3.1<sup>3,7</sup>.1<sup>9,13</sup>.0<sup>12,16</sup>.0<sup>26,30</sup>]tritiacont-3(33),4,6,9(32),10,12,14,23,25,30-decaen-8-yl]acetate**  
 25

Ethyl 3-{3-[(6-hydroxy-2,2-dioxo-2*H*-1,2λ<sup>6</sup>,3-benzoxathiazin-3(4*H*)-yl)methyl]-4-methylphenyl}-3-(1-{2-[(2-hydroxyethyl)(phenyl)amino]ethyl}-4-methyl-1*H*-benzotriazol-5-  
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yl)propanoate (1 eq., 248 mg, 0.3540 mmol) was dissolved in THF (50 mL) and PPh<sub>3</sub> (4 eq., 371 mg, 1.416 mmol) was added. The mixture was cooled to ~5 °C and DIAD (4 eq., 286 mg, 1.416 mmol) was added dropwise. The mixture was heated at reflux temperature for 1h. After completion of the reaction the solvent was evaporated, the crude product was purified via normal  
5 phase silica gel chromatography using heptane-AcOEt (60:40) as an eluent to give the title compound (157 mg, white solid, 65% yield).

The enantiopure final intermediates were obtained by chromatographic separation on chiral column.

<sup>1</sup>H-NMR (500 MHz, DMSO-d<sub>6</sub>) δ ppm: 7.67 (d, 1 H), 7.46 (d, 1 H), 7.45 (dd, 1 H), 7.26 (d, 1  
10 H), 7.25-6.67 (m, 5 H), 7.07 (d, 1 H), 6.9 (dd, 1 H), 6.88 (d, 1 H), 6.1 (d, 1 H), 4.89/4.85 (m+m, 2 H), 4.82 (t, 1 H), 4.13 (s, 2 H), 4.13/3.94 (m+m, 2 H), 4.01/3.93 (d+d, 2 H), 3.9 (q, 2 H), 3.8/3.58 (m+m, 2 H), 3.67/3.42 (m+m, 2 H), 3.1/3.03 (dd+dd, 2 H), 2.72 (s, 3 H), 2.32 (s, 3 H), 0.99 (t, 3 H)

#### 15 **STEP 6 : Preparation of EXAMPLE 58**

Using General Procedure 12 starting from ethyl [4,32-dimethyl-28,28-dioxo-19-phenyl-22,27-dioxa-28λ<sup>6</sup>-thia-1,14,15,16,19-pentaazahexacyclo[21.5.3.1<sup>3,7</sup>.1<sup>9,13</sup>.0<sup>12,16</sup>.0<sup>26,30</sup>]tritiaconta-  
3(33),4,6,9(32),10,12,14,23,25,30-decaen-8-yl]acetate E1 (1 eq.) or E2 (1 eq.) as reactants, the  
20 title compounds (68% - 82% yields respectively) were obtained.

##### **Example 58a (E1)**

HRMS calculated for C<sub>35</sub>H<sub>35</sub>N<sub>5</sub>O<sub>6</sub>S: 653.2308; [M+H]<sup>+</sup> found: 654.236 (δ = -3.2 ppm)

#### 25 **Example 58b (E2)**

HRMS calculated for C<sub>35</sub>H<sub>35</sub>N<sub>5</sub>O<sub>6</sub>S: 653.2308; [M+H]<sup>+</sup> found: 654.2359 (δ = -3.3 ppm)

<sup>1</sup>H-NMR (500 MHz, DMSO-d<sub>6</sub>) δ ppm: 12.13 (brs, 1 H), 7.66 (d, 1 H), 7.46 (dd, 1 H), 7.43 (d, 1 H), 7.27 (d, 1 H), 7.23 (t, 2 H), 7.06 (d, 1 H), 6.89 (dd, 1 H), 6.86 (d, 2 H), 6.84 (d, 1 H), 6.71 (t, 1 H), 6.07 (d, 1 H), 4.88/4.86 (m+m, 2 H), 4.8 (t, 1 H), 4.17/4.09 (d+d, 2 H), 4.15/3.95 (m+m,



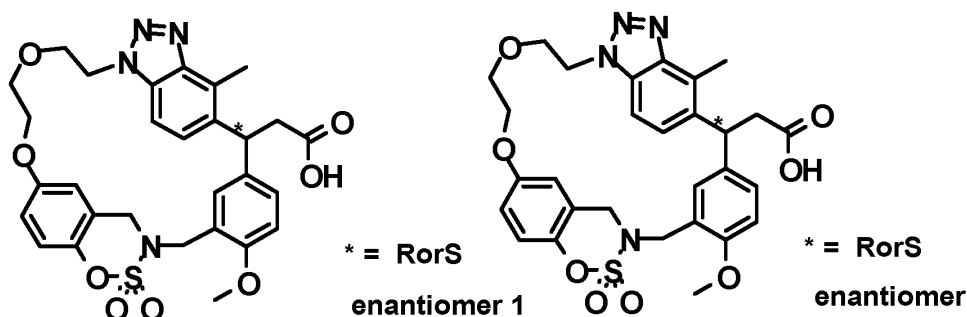
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2 H), 3.99/3.96 (d+d, 2 H), 3.77/3.55 (m+m, 2 H), 3.65/3.4 (m+m, 2 H), 3.02/2.91 (dd+dd, 2 H), 2.72 (s, 3 H), 2.32 (s, 3 H)

<sup>13</sup>C-NMR (125 MHz, DMSO-d<sub>6</sub>) δ ppm: 173.2, 155.6, 147.9, 146.4, 144.9, 141.8, 137.3, 136.3, 132, 132, 131.6, 131.3, 129.8, 128.5, 127.5, 127.3, 119.5, 117.5, 117.4, 116.4, 113.2, 112.5, 108.1, 66.6, 51.9, 50.6, 49.8, 48.5, 46.2, 41.3, 41, 18.4, 13.4

**EXAMPLE 59** : [4-Methoxy-32-methyl-28,28-dioxo-19,22,27-trioxa-28λ<sup>6</sup>-thia-1,14,15,16-tetraazahexacyclo[21.5.3.1<sup>3,7</sup>.1<sup>9,13</sup>.0<sup>12,16</sup>.0<sup>26,30</sup>]tritiaconta-3(33),4,6,9(32),10,12,14,23,25,30-decaen-8-yl]acetic acid

10



**STEP 1** : Preparation of 6-(benzyloxy)-3-[(5-bromo-2-methoxyphenyl)methyl]-3,4-dihydro-2H-1,2λ<sup>6</sup>,3-benzoxathiazine-2,2-dione

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Using General Procedure 7 starting from (5-bromo-2-methoxyphenyl)methanol (1 eq.) and 6-(benzyloxy)-3,4-dihydro-2H-1,2λ<sup>6</sup>,3-benzoxathiazine-2,2-dione (0.77 eq.) as reactants, the title compound (82% yield) was obtained as a white solid.

<sup>1</sup>H-NMR (500 MHz, DMSO-d<sub>6</sub>) δ ppm: 7.49 (dd, 1 H), 7.48-7.29 (m, 5 H), 7.45 (d, 1 H), 7.06 (m, 1 H), 7.01 (m, 1 H), 7.01 (m, 1 H), 6.96 (d, 1 H), 5.08 (s, 2 H), 4.65 (s, 2 H), 4.26 (s, 2 H), 3.72 (s, 3 H)

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**STEP 2 : Preparation of 6-(benzyloxy)-3-([2-methoxy-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]methyl)-3,4-dihydro-2*H*-1,2λ<sup>6</sup>,3-benzoxathiazine-2,2-dione**

5 Using General Procedure 3 starting from 6-(benzyloxy)-3-[(5-bromo-2-methoxyphenyl)methyl]-3,4-dihydro-2*H*-1,2λ<sup>6</sup>,3-benzoxathiazine-2,2-dione (1 eq.) as a reactant, the title compound (87% yield) was obtained as a beige solid.

<sup>1</sup>H-NMR (500 MHz, DMSO-d<sub>6</sub>) δ ppm: 7.66 (dd, 1 H), 7.6 (d, 1 H), 7.44 (d, 2 H), 7.4 (t, 2 H), 7.34 (t, 1 H), 7.08 (d, 1 H), 7.02 (dd, 1 H), 7.02 (d, 1 H), 7 (d, 1 H), 5.07 (s, 2 H), 4.59 (s, 2 H),  
10 4.26 (s, 2 H), 3.75 (s, 3 H), 1.28 (s, 12 H)

**STEP 3 : Preparation of ethyl 3-(3-([6-(benzyloxy)-2,2-dioxo-2*H*-1,2λ<sup>6</sup>,3-benzoxathiazin-3(4*H*)-yl]methyl)-4-methoxyphenyl)-3-(1-{2-[2-(benzyloxy)ethoxy]ethyl}-4-methyl-1*H*-benzotriazol-5-yl)propanoate**

15

Using General Procedure 6 starting from ethyl (2*E*)-3-(1-{2-[2-(benzyloxy)ethoxy]ethyl}-4-methyl-1*H*-benzotriazol-5-yl)prop-2-enoate (1 eq.) and 6-(benzyloxy)-3-([2-methoxy-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]methyl)-3,4-dihydro-2*H*-1,2λ<sup>6</sup>,3-benzoxathiazine-2,2-dione (1.3 eq.) as reactants, the title compound (52% yield) was obtained.

20 <sup>1</sup>H-NMR (500 MHz, DMSO-d<sub>6</sub>) δ ppm: 7.62 (d, 1 H), 7.47-7.14 (m, 12 H), 7.42 (d, 1 H), 6.98 (dd, 1 H), 6.96 (d, 1 H), 6.92 (d, 1 H), 6.84 (d, 1 H), 5.07 (s, 2 H), 4.81 (m, 2 H), 4.81 (t, 1 H), 4.52 (s, 2 H), 4.3 (s, 2 H), 4.19 (s, 2 H), 3.92 (q, 2 H), 3.88 (t, 2 H), 3.64 (s, 3 H), 3.51 (m, 2 H), 3.41 (m, 2 H), 3.13/3.09 (dd+dd, 2 H), 2.75 (s, 3 H), 1 (t, 3 H)

25 **STEP 4 : Preparation of ethyl 3-{3-[(6-hydroxy-2,2-dioxo-2*H*-1,2λ<sup>6</sup>,3-benzoxathiazin-3(4*H*)-yl]methyl)-4-methoxyphenyl}-3-{1-[2-(2-hydroxyethoxy)ethyl]-4-methyl-1*H*-benzotriazol-5-yl}propanoate**

Using General Procedure 8 starting from ethyl 3-(3-([6-(benzyloxy)-2,2-dioxo-2*H*-1,2λ<sup>6</sup>,3-benzoxathiazin-3(4*H*)-yl]methyl)-4-methoxyphenyl)-3-(1-{2-[2-(benzyloxy)ethoxy]ethyl}-4-

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methyl-1*H*-benzotriazol-5-yl)propanoate (1 eq.) as a reactant, the title compound (white solid, quant.) was obtained.

<sup>1</sup>H-NMR (500 MHz, DMSO-d<sub>6</sub>) δ ppm: 9.62 (s, 1 H), 7.64 (d, 1 H), 7.48 (d, 1 H), 7.26 (d, 1 H), 7.23 (dd, 1 H), 6.89 (d, 1 H), 6.85 (d, 1 H), 6.71 (dd, 1 H), 6.59 (d, 1 H), 4.82 (t, 1 H), 4.81 (t, 2 H), 4.55 (m, 1 H), 4.48 (s, 2 H), 4.21/4.17 (d+d, 2 H), 3.94 (q, 2 H), 3.89 (t, 2 H), 3.69 (s, 3 H), 3.38 (m, 4 H), 3.14 (m, 2 H), 2.75 (s, 3 H), 1.02 (t, 3 H)

**STEP 5 : Preparation of ethyl 3-{1-[2-(2-chloroethoxy)ethyl]-4-methyl-1*H*-benzotriazol-5-yl}-3-{3-[(6-hydroxy-2,2-dioxo-2*H*-1,2λ<sup>6</sup>,3-benzoxathiazin-3(4*H*)-yl)methyl]-4-methoxyphenyl}propanoate hydrochloride**

Using General Procedure 10 starting from ethyl 3-{3-[(6-hydroxy-2,2-dioxo-2*H*-1,2λ<sup>6</sup>,3-benzoxathiazin-3(4*H*)-yl)methyl]-4-methoxyphenyl}-3-{1-[2-(2-hydroxyethoxy)ethyl]-4-methyl-1*H*-benzotriazol-5-yl}propanoate (1 eq.) as a reactant, the title compound (solid foam, 96% yield) was obtained.

<sup>1</sup>H-NMR (500 MHz, DMSO-d<sub>6</sub>) δ ppm: 9.64 (brs, 1 H), 7.64 (d, 1 H), 7.49 (d, 1 H), 7.26 (d, 1 H), 7.22 (dd, 1 H), 6.89 (d, 1 H), 6.84 (d, 1 H), 6.71 (dd, 1 H), 6.59 (d, 1 H), 4.83 (t, 2 H), 4.81 (t, 1 H), 4.47 (s, 2 H), 4.2/4.17 (d+d, 2 H), 3.94 (q, 2 H), 3.93 (t, 2 H), 3.69 (s, 3 H), 3.6 (t, 2 H), 3.59 (t, 2 H), 3.14 (d, 2 H), 2.75 (s, 3 H), 1.02 (t, 3 H)

**STEP 6 : Preparation of ethyl [4-methoxy-32-methyl-28,28-dioxo-19,22,27-trioxa-28λ<sup>6</sup>-thia-1,14,15,16-tetraazahexacyclo[21.5.3.1<sup>3,7</sup>.1<sup>9,13</sup>.0<sup>12,16</sup>.0<sup>26,30</sup>]tritiaconta-3(33),4,6,9(32),10,12,14,23,25,30-decaen-8-yl]acetate**

Using General Procedure 11 starting from ethyl 3-{1-[2-(2-chloroethoxy)ethyl]-4-methyl-1*H*-benzotriazol-5-yl}-3-{3-[(6-hydroxy-2,2-dioxo-2*H*-1,2λ<sup>6</sup>,3-benzoxathiazin-3(4*H*)-yl)methyl]-4-methoxyphenyl}propanoate hydrochloride (1 eq.) as a reactant, the title compound (59% yield) was obtained.

The enantiopure final intermediates were obtained by chromatographic separation on chiral column.

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<sup>1</sup>H-NMR (500 MHz, DMSO-d<sub>6</sub>) δ ppm: 7.71 (d, 1 H), 7.38 (dd, 1 H), 7.35 (d, 1 H), 6.96 (d, 1 H), 6.95 (d, 1 H), 6.94 (d, 1 H), 6.82 (dd, 1 H), 6.46 (d, 1 H), 4.86/4.83 (m+m, 2 H), 4.79 (t, 1 H), 4.4/4.23 (d+d, 2 H), 4.18 (s, 2 H), 3.99/3.94 (m+m, 2 H), 3.94 (m, 2 H), 3.89 (m, 2 H), 3.81/3.68 (m+m, 2 H), 3.76 (s, 3 H), 3.09/3.04 (dd+dd, 2 H), 2.7 (s, 3 H), 0.98 (t, 3 H)

5

**STEP 7 : Preparation of EXAMPLE 59**

Using General Procedure 12 starting from ethyl [4-methoxy-32-methyl-28,28-dioxo-19,22,27-trioxa-28λ<sup>6</sup>-thia-1,14,15,16-tetraazahexacyclo[21.5.3.1<sup>3,7</sup>.1<sup>9,13</sup>.0<sup>12,16</sup>.0<sup>26,30</sup>]tritiaconta-  
10 3(33),4,6,9(32),10,12,14,23,25,30-decaen-8-yl]acetate E1 (1 eq.) or E2 (1 eq.) as reactants, the title compounds (91% - 93% yields respectively) were obtained.

**Example 59a (E1)**

HRMS calculated for C<sub>29</sub>H<sub>30</sub>N<sub>4</sub>O<sub>8</sub>S: 594.1784; [M+H]<sup>+</sup> found: 595.1843 (δ = -2.4 ppm)

15

**Example 59b (E2)**

HRMS calculated for C<sub>29</sub>H<sub>30</sub>N<sub>4</sub>O<sub>8</sub>S: 594.1784; [M+H]<sup>+</sup> found: 595.1849 (δ = -1.4 ppm)

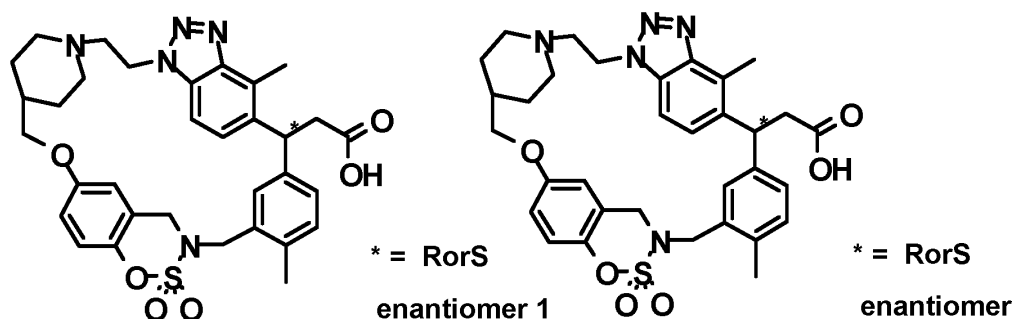
<sup>1</sup>H-NMR (500 MHz, DMSO-d<sub>6</sub>) δ ppm: 12.05 (brs, 1 H), 7.71 (d, 1 H), 7.4 (dd, 1 H), 7.34 (d, 1 H), 6.96 (d, 1 H), 6.95 (d, 1 H), 6.92 (d, 1 H), 6.82 (dd, 1 H), 6.44 (d, 1 H), 4.84 (m, 2 H), 4.77  
20 (t, 1 H), 4.39/4.22 (d+d, 2 H), 4.18 (s, 2 H), 4/3.95 (m+m, 2 H), 3.94 (m, 2 H), 3.81/3.68 (m+m, 2 H), 3.77 (s, 3 H), 2.96 (d, 2 H), 2.7 (s, 3 H)

<sup>13</sup>C-NMR (125 MHz, DMSO-d<sub>6</sub>) δ ppm: 173.2, 157, 155.6, 146.5, 145.2, 136.7, 135.7, 132.5, 131, 131, 127.1, 126.6, 121.3, 118.7, 118.2, 115, 114.4, 111.8, 109.2, 69.9, 68.6, 68.3, 56.1, 48.9, 48.8, 48.5, 41.3, 41.1, 13.3

25

**EXAMPLE 60** : [4,36-Dimethyl-30,30-dioxo-24,29-dioxa-30λ<sup>6</sup>-thia-1,14,15,16,19-pentaazaheptacyclo[23.5.3.2<sup>19,22</sup>.1<sup>3,7</sup>.1<sup>9,13</sup>.0<sup>12,16</sup>.0<sup>28,32</sup>]heptatriaconta-  
3(37),4,6,9(36),10,12,14,25,27,32-decaen-8-yl]acetic acid

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**STEP 1 : Preparation of ethyl 3-{3-[(6-hydroxy-2,2-dioxo-2*H*-1,2λ<sup>6</sup>,3-benzoxathiazin-3(4*H*)-yl)methyl]-4-methylphenyl}-3-[1-(2-hydroxyethyl)-4-methyl-1*H*-benzotriazol-5-yl]propanoate**

Using General Procedure 8 starting from ethyl 3-(3-{[6-(benzyloxy)-2,2-dioxo-2*H*-1,2λ<sup>6</sup>,3-benzoxathiazin-3(4*H*)-yl)methyl]-4-methylphenyl}-3-[1-(2-hydroxyethyl)-4-methyl-1*H*-benzotriazol-5-yl]propanoate (1 eq.) as a reactant, the title compound (white solid, 94% yield) was obtained.

**<sup>1</sup>H-NMR** (500 MHz, DMSO-*d*<sub>6</sub>) δ ppm: 9.71 (s, 1 H), 7.6 (d, 1 H), 7.49 (d, 1 H), 7.23 (d, 1 H), 7.18 (dd, 1 H), 7.13 (d, 1 H), 7 (d, 1 H), 6.79 (dd, 1 H), 6.62 (d, 1 H), 4.96 (t, 1 H), 4.84 (t, 1 H), 4.67 (t, 2 H), 4.41/4.36 (d+d, 2 H), 4.21/4.17 (d+d, 2 H), 3.94 (q, 2 H), 3.84 (q, 2 H), 3.19/3.15 (dd+dd, 2 H), 2.76 (s, 3 H), 2.22 (s, 3 H), 1.03 (t, 3 H)

**STEP 2 : Preparation of ethyl 3-[1-(2-chloroethyl)-4-methyl-1*H*-benzotriazol-5-yl]-3-{3-[(6-hydroxy-2,2-dioxo-2*H*-1,2λ<sup>6</sup>,3-benzoxathiazin-3(4*H*)-yl)methyl]-4-methylphenyl}propanoate hydrochloride**

Using General Procedure 10 starting from ethyl 3-{3-[(6-hydroxy-2,2-dioxo-2*H*-1,2λ<sup>6</sup>,3-benzoxathiazin-3(4*H*)-yl)methyl]-4-methylphenyl}-3-[1-(2-hydroxyethyl)-4-methyl-1*H*-benzotriazol-5-yl]propanoate (1 eq.) as a reactant, the title compound (off-white solid foam, 96% yield) was obtained. The product was used in the next step without further purification.

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<sup>1</sup>H-NMR (500 MHz, DMSO-d<sub>6</sub>) δ ppm: 9.72 (br., 1 H), 7.67 (d, 1 H), 7.53 (d, 1 H), 7.24 (d, 1 H), 7.2 (dd, 1 H), 7.13 (d, 1 H), 6.99 (d, 1 H), 6.79 (dd, 1 H), 6.61 (d, 1 H), 5.02 (t, 2 H), 4.84 (t, 1 H), 4.4/4.36 (d+d, 2 H), 4.22/4.17 (d+d, 2 H), 4.15 (t, 2 H), 3.93 (q, 2 H), 3.18 (d, 2 H), 2.77 (s, 3 H), 2.22 (s, 3 H), 1 (t, 3 H)

5

**STEP 3 : Preparation of ethyl 3-{3-[(6-hydroxy-2,2-dioxo-2*H*-1,2λ<sup>6</sup>,3-benzoxathiazin-3(4*H*)-yl)methyl]-4-methylphenyl}-3-(1-{2-[4-(hydroxymethyl)piperidin-1-yl]ethyl}-4-methyl-1*H*-benzotriazol-5-yl)propanoate**

10 To a stirred mixture of ethyl 3-[1-(2-chloroethyl)-4-methyl-1*H*-benzotriazol-5-yl]-3-{3-[(6-hydroxy-2,2-dioxo-2*H*-1,2λ<sup>6</sup>,3-benzoxathiazin-3(4*H*)-yl)methyl]-4-methylphenyl} propanoate hydrochloride (1 eq., 0.8 g, 1.335 mmol) in DMF (8 mL) (piperidin-4-yl)methanol (10 eq., 1.538 g, 13.35 mmol) was added at RT. The reaction mixture was heated to 80 °C and stirred at this temperature for 24 h. After completion of the reaction the mixture was cooled to RT and it  
15 was directly injected to a C18 column and purified by reversed-phase chromatography using aq. 5 mM NH<sub>4</sub>HCO<sub>3</sub> solution-MeCN gradient elution to give the title compound (393 mg, white solid, 43% yield).

<sup>1</sup>H-NMR (500 MHz, DMSO-d<sub>6</sub>) δ ppm: 9.73 (brs, 1 H), 7.62 (d, 1 H), 7.5 (d, 1 H), 7.22 (d, 1 H), 7.19 (dd, 1 H), 7.13 (d, 1 H), 6.99 (d, 1 H), 6.79 (dd, 1 H), 6.6 (d, 1 H), 4.83 (t, 1 H), 4.74  
20 (t, 2 H), 4.56/0.96 (m+m, 4 H), 4.4/4.35 (d+d, 2 H), 4.37 (brs, 1 H), 4.22/4.17 (d+d, 2 H), 3.93 (q, 2 H), 3.17 (d, 2 H), 3.17 (d, 2 H), 2.9/2.85/1.92 (d/d+t, 4 H), 2.77 (t, 2 H), 2.75 (s, 3 H), 2.22 (s, 3 H), 1.27 (m, 1 H), 0.99 (t, 3 H)

**STEP 4 : Preparation of ethyl [4,36-dimethyl-30,30-dioxo-24,29-dioxa-30λ<sup>6</sup>-thia-1,14,15,16,19-pentaazaheptacyclo[23.5.3.2<sup>19,22</sup>.1<sup>3,7</sup>.1<sup>9,13</sup>.0<sup>12,16</sup>.0<sup>28,32</sup>]heptatriaconta-3(37),4,6,9(36),10,12,14,25,27,32-decaen-8-yl]acetate**

25

Ethyl 3-{3-[(6-hydroxy-2,2-dioxo-2*H*-1,2λ<sup>6</sup>,3-benzoxathiazin-3(4*H*)-yl)methyl]-4-methylphenyl}-3-(1-{2-[4-(hydroxymethyl)piperidin-1-yl]ethyl}-4-methyl-1*H*-benzotriazol-5-  
30

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yl)propanoate (1 eq., 287 mg, 0.4237 mmol) was dissolved in THF (60 mL) and PPh<sub>3</sub> (4 eq., 444 mg, 1.694 mmol) was added. The mixture was cooled to ~5 °C and DIAD (4 eq., 343 mg, 1.694 mmol) was added dropwise. After heating at reflux temperature for 1.5h. the solvent was evaporated, the crude product was dissolved in DMF and the mixture was directly injected to a C18 column and purified by reversed-phase chromatography using aq. 5 mM NH<sub>4</sub>HCO<sub>3</sub> solution-MeCN gradient elution to give the title compound (100 mg, 36% yield).

The enantiopure final intermediates were obtained by chromatographic separation on chiral column.

<sup>1</sup>H-NMR (500 MHz, DMSO-d<sub>6</sub>) δ ppm: 7.68 (d, 1 H), 7.61 (d, 1 H), 7.42 (dd, 1 H), 7.25 (d, 1 H), 7.04 (d, 1 H), 7.01 (d, 1 H), 6.99 (d, 1 H), 6.96 (dd, 1 H), 4.84/4.61 (td+dd, 2 H), 4.8 (t, 1 H), 4.35/4.24 (d+d, 2 H), 4.24/4.12 (d+d, 2 H), 4.07/3.93 (dd+dd, 2 H), 3.88 (q, 2 H), 3.14/2.99 (dd+dd, 2 H), 3.02/2.76 (t+dd, 2 H), 3.01/2.64/2.06/1.72 (dd+t+dd+t, 4 H), 2.67 (s, 3 H), 2.33 (s, 3 H), 1.57 (m, 1 H), 1.47/1.42/1.28/1.12 (d+dd+d+dd, 4 H), 0.97 (t, 3 H)

#### 15 STEP 5 : Preparation of EXAMPLE 60

Using General Procedure 12 starting from ethyl [4,36-dimethyl-30,30-dioxo-24,29-dioxa-30λ<sup>6</sup>-thia-1,14,15,16,19-pentaazaheptacyclo[23.5.3.2<sup>19,22</sup>.1<sup>3,7</sup>.1<sup>9,13</sup>.0<sup>12,16</sup>.0<sup>28,32</sup>]heptatriaconta-3(37),4,6,9(36),10,12,14,25,27,32-decaen-8-yl]acetate E1 (1 eq.) or E2 (1 eq.) as reactants, the title compounds (48% - 44% yields respectively) were obtained.

#### Example 60a (E1)

HRMS calculated for C<sub>33</sub>H<sub>37</sub>N<sub>5</sub>O<sub>6</sub>S: 631.2464; [M+H]<sup>+</sup> found: 632.2538 (δ = 0.1 ppm)

#### 25 Example 60b (E2)

HRMS calculated for C<sub>33</sub>H<sub>37</sub>N<sub>5</sub>O<sub>6</sub>S: 631.2464; [M+H]<sup>+</sup> found: 632.2542 (δ = 0.7 ppm)

<sup>1</sup>H-NMR (500 MHz, DMSO-d<sub>6</sub>) δ ppm: 12.29 (brs, 1 H), 7.69 (d, 1 H), 7.6 (d, 1 H), 7.43 (dd, 1 H), 7.25 (d, 1 H), 7.04 (d, 1 H), 7.01 (d, 1 H), 6.97 (d, 1 H), 6.95 (dd, 1 H), 4.84/4.6 (dd+d, 2 H), 4.78 (t, 1 H), 4.34/4.24 (d+d, 2 H), 4.25/4.11 (d+d, 2 H), 4.06/3.93 (dd+dd, 2 H), 3.04/2.77

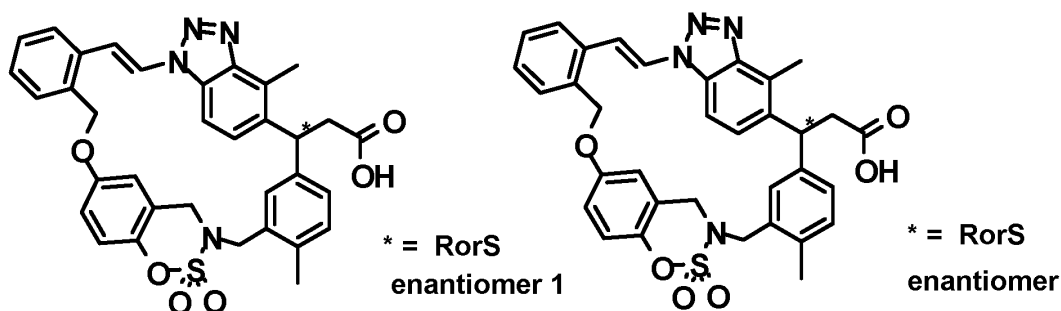
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(t+dd, 2 H), 3.03/2.9 (dd+dd, 2 H), 3.01/2.64/2.07/1.72 (dd+t+dd+t, 4 H), 2.66 (s, 3 H), 2.34 (s, 3 H), 1.57 (m, 1 H), 1.47/1.43/1.28/1.12 (d+dd+d+dd, 4 H)

<sup>13</sup>C-NMR (125 MHz, DMSO-d<sub>6</sub>) δ ppm: 173, 157.1, 146.4, 144.4, 141.9, 136.6, 136.2, 132.7, 132.5, 131.6, 129.9, 129.8, 126.9, 126.6, 119.2, 118.1, 116.1, 113.7, 109.2, 71.5, 57.9, 53.4/51.9, 52.3, 49.2, 46, 42.2, 41.7, 36.5, 28.9/28.2, 18.9, 13.3

**EXAMPLE 61** : [(17*E*)-4,36-dimethyl-32,32-dioxo-26,31-dioxa-32λ<sup>6</sup>-thia-1,14,15,16-tetraazaheptacyclo[25.5.3.1<sup>3,7</sup>.1<sup>9,13</sup>.0<sup>12,16</sup>.0<sup>19,24</sup>.0<sup>30,34</sup>]heptatriaconta-3(37),4,6,9(36),10,12,14,17,19,21,23,27,29,34-tetradecaen-8-yl]acetic acid

10



**STEP 1: Preparation of ethyl 3-(1-ethenyl-4-methyl-1*H*-benzotriazol-5-yl)-3-{3-[(6-hydroxy-2,2-dioxo-2*H*-1,2λ<sup>6</sup>,3-benzoxathiazin-3(4*H*)-yl)methyl]-4-methylphenyl}propanoate**

15

To the stirred solution of ethyl 3-[1-(2-chloroethyl)-4-methyl-benzotriazol-5-yl]-3-[3-[(6-hydroxy-2,2-dioxo-4*H*-1,2λ<sup>6</sup>,3-benzoxathiazin-3-yl)methyl]-4-methyl-phenyl]propanoate hydrochloride (1 eq., 1.5 g, 2.36 mmol) in MeCN (25 mL) Cs<sub>2</sub>CO<sub>3</sub> (3 eq., 2.31 g, 7.08 mmol) was added and the mixture was stirred overnight at 80 °C. After the completion of the reaction the solvent was evaporated under reduced pressure. The residue was partitioned between 50 mL DCM / 50 mL water, the layers were separated, the aq. layer was extracted with further 2x30 mL DCM. The combined organic layer was dried over MgSO<sub>4</sub>, filtered and the filtrate was concentrated to dryness. The crude product was purified by reversed-phase chromatography

20



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using aq. 5 mM NH<sub>4</sub>HCO<sub>3</sub> solution-MeCN gradient elution to give the title compound (848 mg, 64% yield).

**<sup>1</sup>H-NMR** (500 MHz, DMSO-d<sub>6</sub>) δ ppm: 9.7 (s, 1 H), 7.82 (d, 1 H), 7.82 (dd, 1 H), 7.62 (d, 1 H), 7.23 (d, 1 H), 7.2 (dd, 1 H), 7.14 (d, 1 H), 6.99 (d, 1 H), 6.78 (dd, 1 H), 6.61 (d, 1 H),  
5 5.97/5.29 (dd+dd, 2 H), 4.85 (t, 1 H), 4.41/4.36 (d+d, 2 H), 4.22/4.17 (d+d, 2 H), 3.94 (q, 2 H),  
3.19 (d, 2 H), 2.79 (s, 3 H), 2.22 (s, 3 H), 1.01 (t, 3 H)

**STEP 2 : Preparation of ethyl 3-{3-[(6-hydroxy-2,2-dioxo-2*H*-1,2λ<sup>6</sup>,3-benzoxathiazin-3(4*H*)-yl)methyl]-4-methylphenyl}-3-(1-{(*E*)-2-[2-(hydroxymethyl)phenyl]ethenyl}-4-methyl-1*H*-benzotriazol-5-yl)propanoate**  
10

To the stirred solution of ethyl 3-(1-ethenyl-4-methyl-1*H*-benzotriazol-5-yl)-3-{3-[(6-hydroxy-2,2-dioxo-2*H*-1,2λ<sup>6</sup>,3-benzoxathiazin-3(4*H*)-yl)methyl]-4-methylphenyl}propanoate (1 eq., 0.844 g, 1.5 mmol) in MeCN (8 mL) TEA (38 eq., 8 mL, 57.4 mmol), (2-iodophenyl)methanol  
15 (2 eq., 702 mg, 3 mmol), PPh<sub>3</sub> (0.2 eq., 79 mg, 0.3 mmol) and palladium(II) acetate catalyst (0.1 eq., 34 mg, 0.15 mmol) were added. The mixture was flushed with nitrogen and heated in a microwave reactor at 110 °C for 4h. After completion of the reaction the solvent was evaporated under reduced pressure. The residue was partitioned between 50 mL DCM / 50 mL water, the layers were separated, then the aq. layer was extracted with 50 mL DCM. The combined organic  
20 layer was dried over MgSO<sub>4</sub>, filtered and the filtrate was concentrated to dryness. The crude product was purified by normal phase silica gel chromatography using DCM-MeOH (100:0 to 99:1) as an eluent to give the title compound (808 mg, 81% yield).

**<sup>1</sup>H-NMR** (500 MHz, DMSO-d<sub>6</sub>) δ ppm: 9.69 (s, 1 H), 8.29 (d, 1 H), 7.94 (d, 1 H), 7.86 (dd, 1 H), 7.76 (d, 1 H), 7.65 (d, 1 H), 7.43 (dd, 1 H), 7.36 (td, 1 H), 7.33 (td, 1 H), 7.26 (d, 1 H), 7.21  
25 (dd, 1 H), 7.15 (d, 1 H), 6.99 (d, 1 H), 6.79 (dd, 1 H), 6.61 (d, 1 H), 5.3 (t, 1 H), 4.87 (t, 1 H),  
4.66 (d, 2 H), 4.42/4.38 (d+d, 2 H), 4.23/4.19 (d+d, 2 H), 3.95 (q, 2 H), 3.21 (d, 2 H), 2.81 (s, 3 H), 2.23 (s, 3 H), 1.02 (t, 3 H)

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**STEP 3 : Preparation of ethyl 3-(1-{{(E)-2-[2-(chloromethyl)phenyl]ethenyl}-4-methyl-1H-benzotriazol-5-yl}-3-{3-[(6-hydroxy-2,2-dioxo-2H-1,2λ<sup>6</sup>,3-benzoxathiazin-3(4H)-yl)methyl]-4-methylphenyl} propanoate hydrochloride**

5 Using General Procedure 10 starting from ethyl 3-{3-[(6-hydroxy-2,2-dioxo-2H-1,2λ<sup>6</sup>,3-benzoxathiazin-3(4H)-yl)methyl]-4-methylphenyl}-3-(1-{{(E)-2-[2-(hydroxymethyl)phenyl]ethenyl}-4-methyl-1H-benzotriazol-5-yl})propanoate (1 eq.) as a reactant, the title compound (yellow solid foam, quant.) was obtained. The product was used in the next step without further purification.

10 **<sup>1</sup>H-NMR** (500 MHz, DMSO-d<sub>6</sub>) δ ppm: 9.71 (brs, 1 H), 8.39 (d, 1 H), 7.98 (d, 1 H), 7.96 (dm, 1 H), 7.78 (d, 1 H), 7.68 (d, 1 H), 7.51 (dm, 1 H), 7.46 (m, 1 H), 7.36 (m, 1 H), 7.27 (d, 1 H), 7.22 (dd, 1 H), 7.15 (d, 1 H), 6.99 (d, 1 H), 6.79 (dd, 1 H), 6.61 (d, 1 H), 5 (s, 2 H), 4.87 (t, 1 H), 4.41/4.38 (d+d, 2 H), 4.23/4.18 (d+d, 2 H), 3.95 (q, 2 H), 3.21 (d, 2 H), 2.82 (s, 3 H), 2.23 (s, 3 H), 1.02 (t, 3 H)

15

**STEP 4 : Preparation of ethyl [(17E)-4,36-dimethyl-32,32-dioxo-26,31-dioxa-32λ<sup>6</sup>-thia-1,14,15,16-tetraazaheptacyclo[25.5.3.1<sup>3,7</sup>.1<sup>9,13</sup>.0<sup>12,16</sup>.0<sup>19,24</sup>.0<sup>30,34</sup>]heptatriaconta-3(37),4,6,9(36),10,12,14,17,19,21,23,27,29,34-tetradecaen-8-yl]acetate**

20 Using General Procedure 11 starting from ethyl 3-(1-{{(E)-2-[2-(chloromethyl)phenyl]ethenyl}-4-methyl-1H-benzotriazol-5-yl}-3-{3-[(6-hydroxy-2,2-dioxo-2H-1,2λ<sup>6</sup>,3-benzoxathiazin-3(4H)-yl)methyl]-4-methylphenyl} propanoate hydrochloride (1 eq.) as a reactant, the title compound (13% yield) was obtained.

The enantiopure final intermediates were obtained by chromatographic separation on chiral  
25 column.

**<sup>1</sup>H-NMR** (500 MHz, DMSO-d<sub>6</sub>) δ ppm: 8.42 (d, 1 H), 8 (d, 1 H), 7.83 (d, 1 H), 7.66 (d, 1 H), 7.64 (d, 1 H), 7.55 (d, 1 H), 7.51 (t, 1 H), 7.45 (dd, 1 H), 7.41 (t, 1 H), 7.24 (dd, 1 H), 7.23 (d, 1 H), 7.21 (d, 1 H), 7.02 (d, 1 H), 6.92 (d, 1 H), 5.26/5.16 (d+d, 2 H), 4.89 (dd, 1 H), 4.32/4.11 (d+d, 2 H), 4.28/4.08 (d+d, 2 H), 3.89 (q, 2 H), 3.23/3.08 (dd+dd, 2 H), 2.8 (s, 3 H), 2.31 (s, 3  
30 H), 0.96 (t, 3 H)

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**STEP 5 : Preparation of EXAMPLE 61**

Using General Procedure 12 starting from ethyl [(17*E*)-4,36-dimethyl-32,32-dioxo-26,31-dioxa-32 $\lambda^6$ -thia-1,14,15,16-tetraazaheptacyclo[25.5.3.1<sup>3,7</sup>.1<sup>9,13</sup>.0<sup>12,16</sup>.0<sup>19,24</sup>.0<sup>30,34</sup>]heptatriaconta-3(37),4,6,9(36),10,12,14,17,19,21,23,27,29,34-tetradecaen-8-yl]acetate E1 (1 eq.) or E2 (1 eq.) as reactants, the title compounds (89% - 73% yields respectively) were obtained.

**Example 61a (E1)**

10 **HRMS** calculated for C<sub>34</sub>H<sub>30</sub>N<sub>4</sub>O<sub>6</sub>S: 622.1886; [M+H]<sup>+</sup> found: 623.1956 ( $\delta$  = -0.5 ppm)

**Example 61b (E2)**

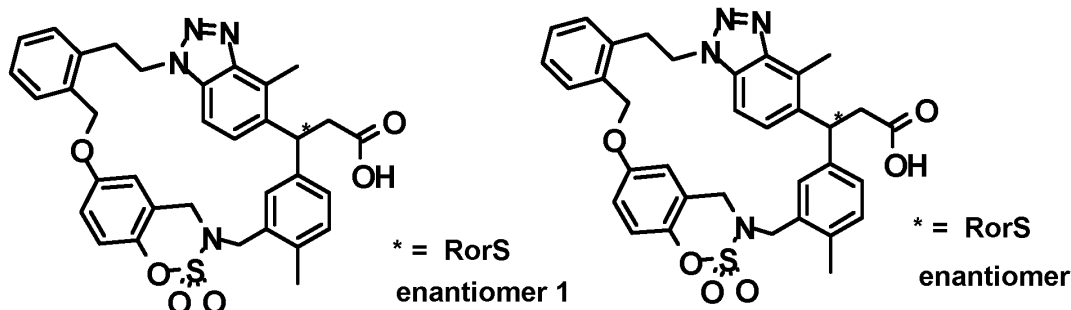
**HRMS** calculated for C<sub>34</sub>H<sub>30</sub>N<sub>4</sub>O<sub>6</sub>S: 622.1886; [M+H]<sup>+</sup> found: 623.1955 ( $\delta$  = -0.6 ppm)

**<sup>1</sup>H-NMR** (500 MHz, DMSO-d<sub>6</sub>)  $\delta$  ppm: 8.42 (d, 1 H), 8 (d, 1 H), 7.81 (d, 1 H), 7.63 (d, 1 H),  
15 7.6 (d, 1 H), 7.55 (d, 1 H), 7.51 (t, 1 H), 7.44 (dd, 1 H), 7.41 (t, 1 H), 7.24 (dd, 1 H), 7.22 (d, 1 H),  
7.2 (d, 1 H), 6.99 (d, 1 H), 6.92 (d, 1 H), 5.26/5.15 (d+d, 2 H), 4.87 (t, 1 H), 4.34/4.11 (d+d,  
2 H), 4.28/4.09 (d+d, 2 H), 3.09/2.94 (dd+dd, 2 H), 2.8 (s, 3 H), 2.31 (s, 3 H)

**<sup>13</sup>C-NMR** (125 MHz, DMSO-d<sub>6</sub>)  $\delta$  ppm: 173.4, 156, 146.9, 145.5, 141.7, 138.3, 136.2, 135,  
134.4, 132.1, 131.3, 131.3, 130.5, 129.9, 129.6, 129.2, 128.9, 128.8, 128.2, 126.3, 125.6, 119.9,  
20 119.5, 118.6, 116.1, 115.4, 109.4, 70.8, 52, 48.7, 41.9, 40.9, 18.5, 13.3

**EXAMPLE 62** : [4,36-Dimethyl-32,32-dioxo-26,31-dioxa-32 $\lambda^6$ -thia-1,14,15,16-tetraazaheptacyclo[25.5.3.1<sup>3,7</sup>.1<sup>9,13</sup>.0<sup>12,16</sup>.0<sup>19,24</sup>.0<sup>30,34</sup>]heptatriaconta-3(37),4,6,9(36),10,12,14,19,21,23,27,29,34-tridecaen-8-yl]acetic acid

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Ethyl [(17*E*)-4,36-dimethyl-32,32-dioxo-26,31-dioxo-32λ<sup>6</sup>-thia-1,14,15,16-tetraazaheptacyclo  
[25.5.3.1<sup>3,7</sup>.1<sup>9,13</sup>.0<sup>12,16</sup>.0<sup>19,24</sup>.0<sup>30,34</sup>]heptatriaconta-

- 5 3(37),4,6,9(36),10,12,14,17,19,21,23,27,29,34-tetradecaen-8-yl]acetate (1 eq., 49 mg, 0.075 mmol) and Pd/C catalyst (0.1 eq., 4 mg) were suspended in dioxane (5 mL) and hydrogenated in a stainless steel reaction vessel under atmospheric pressure at RT for 3.5 h. The mixture was filtered through a Celite pad and evaporated to dryness. The crude product was reacted using General Procedure 12 to give the title compound (white solid, 61% yield).
- 10 The enantiopure products were obtained by chromatographic separation on chiral column.

#### **Example 62a (E1)**

HRMS calculated for C<sub>34</sub>H<sub>32</sub>N<sub>4</sub>O<sub>6</sub>S: 624.2042; [M+H]<sup>+</sup> found: 625.2141 (δ = 4.1 ppm)

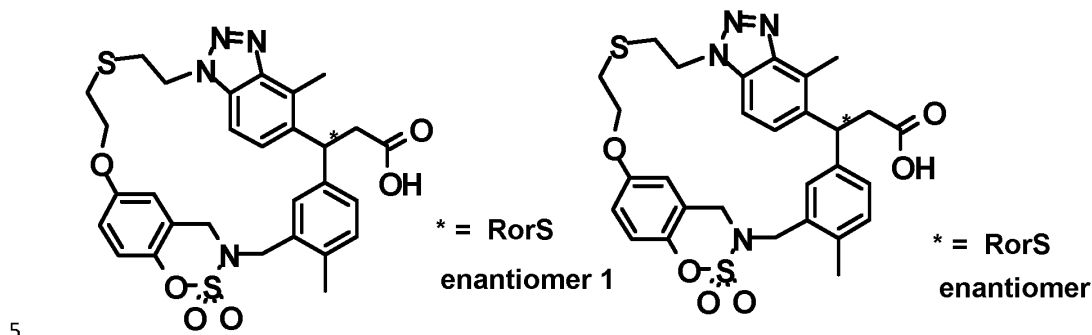
#### **Example 62b (E2)**

HRMS calculated for C<sub>34</sub>H<sub>32</sub>N<sub>4</sub>O<sub>6</sub>S: 624.2042; [M+H]<sup>+</sup> found: 625.2128 (δ = 2.0 ppm)

- <sup>1</sup>H-NMR (500 MHz, DMSO-d<sub>6</sub>) δ ppm: 7.75 (d, 1 H), 7.62 (d, 1 H), 7.48 (d, 1 H), 7.48 (d, 1 H), 7.46 (t, 1 H), 7.38 (d, 1 H), 7.33 (t, 1 H), 7.27 (d, 1 H), 7.1 (d, 1 H), 7.03 (dd, 1 H), 6.71 (brs., 1 H), 6.53 (d, 1 H), 4.92 (m, 2 H), 4.83 (t, 1 H), 4.74/4.69 (d+d, 2 H), 4.3/3.96 (d+d, 2 H),  
20 4.18/4.02 (d+d, 2 H), 3.43/3.16 (m+m, 2 H), 3.11/2.85 (dd+dd, 2 H), 2.71 (s, 3 H), 2.33 (s, 3 H)
- <sup>13</sup>C-NMR (125 MHz, DMSO-d<sub>6</sub>) δ ppm: 131.5, 131.3, 130.5, 130.2, 129.5, 128.4, 127.8, 127.3, 119.6, 116, 112.8, 108, 69.2, 52, 48.8, 48.8, 41.4, 40.9, 32.2, 18.4, 13.3

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**EXAMPLE 63** : [4,32-Dimethyl-28,28-dioxo-22,27-dioxa-19,28 $\lambda^6$ -dithia-1,14,15,16-tetraazahexacyclo[21.5.3.1<sup>3,7</sup>.1<sup>9,13</sup>.0<sup>12,16</sup>.0<sup>26,30</sup>]tritiaconta-3(33),4,6,9(32),10,12,14,23,25,30-decaen-8-yl]acetic acid



**STEP 1** : Preparation of ethyl 3-{3-[(6-hydroxy-2,2-dioxo-2*H*-1,2 $\lambda^6$ ,3-benzoxathiazin-3(4*H*)-yl)methyl]-4-methylphenyl}-3-(1-{2-[(2-hydroxyethyl)sulfanyl]ethyl}-4-methyl-1*H*-benzotriazol-5-yl)propanoate

10

Ethyl 3-[1-(2-chloroethyl)-4-methyl-1*H*-benzotriazol-5-yl]-3-{3-[(6-hydroxy-2,2-dioxo-2*H*-1,2 $\lambda^6$ ,3-benzoxathiazin-3(4*H*)-yl)methyl]-4-methylphenyl} propanoate hydrochloride (1 eq., 0.836 g, 1.395 mmol) and K<sub>2</sub>CO<sub>3</sub> (2.2 eq., 424 mg, 3.070 mmol) were suspended in EtOH (50 mL). Potassium iodide (0.1 eq., 23 mg, 0.1395 mmol) and 2-sulfanylethan-1-ol (15 eq., 1.64 g, 20.93 mmol) were added at RT and the mixture was heated at 60 °C for 6 days. After cooling to Rt, the reaction mixture was filtered and concentrated to dryness to give the crude product, which was purified via normal phase silica gel chromatography using DCM-MeOH (100:0 to 95:5) as eluents to give the title compound (yellow oil, 400 mg, 45% yield).

15

<sup>1</sup>H-NMR (500 MHz, DMSO-d<sub>6</sub>)  $\delta$  ppm: 9.71 (s, 1 H), 7.65 (d, 1 H), 7.51 (d, 1 H), 7.23 (d, 1 H), 7.19 (dd, 1 H), 7.13 (d, 1 H), 6.99 (d, 1 H), 6.79 (dd, 1 H), 6.6 (d, 1 H), 4.86 (t, 1 H), 4.84 (dd, 1 H), 4.83 (t, 2 H), 4.4/4.36 (d+d, 2 H), 4.22/4.17 (d+d, 2 H), 3.94 (q, 2 H), 3.52 (q, 2 H), 3.19/3.15 (dd+dd, 2 H), 3.09 (t, 2 H), 2.76 (s, 3 H), 2.58 (t, 2 H), 2.22 (s, 3 H), 1.01 (t, 3 H)

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**STEP 2 : Preparation of ethyl [4,32-dimethyl-28,28-dioxo-22,27-dioxa-19,28 $\lambda^6$ -dithia-1,14,15,16-tetraazahexacyclo[21.5.3.1<sup>3,7</sup>.1<sup>9,13</sup>.0<sup>12,16</sup>.0<sup>26,30</sup>]tritriaconta-3(33),4,6,9(32),10,12,14,23,25,30-decaen-8-yl]acetate**

5 Ethyl 3-{3-[(6-hydroxy-2,2-dioxo-2*H*-1,2 $\lambda^6$ ,3-benzoxathiazin-3(4*H*)-yl)methyl]-4-methylphenyl}-3-(1-{2-[(2-hydroxyethyl)sulfanyl]ethyl}-4-methyl-1*H*-benzotriazol-5-yl)propanoate (1 eq., 400 mg, 0.624 mmol) was dissolved in THF (20 mL). PPh<sub>3</sub> (4 eq., 655 mg, 2.497 mmol) was added and the mixture was cooled to ~5°C. DIAD (4 eq., 504.9 mg, 2.497 mmol) was added dropwise and the mixture was stirred at RT for 2 h. After completion of the  
10 reaction the mixture was concentrated to dryness to give the crude product, which was purified via preparative reversed-phase chromatography using 5 mM aq. NH<sub>4</sub>HCO<sub>3</sub> solution-MeCN as eluents to give the title compound (215 mg, white solid, 55% yield).

The enantiopure final intermediates were obtained by chromatographic separation on chiral column.

15 <sup>1</sup>H-NMR (500 MHz, DMSO-d<sub>6</sub>)  $\delta$  ppm: 7.72 (d, 1 H), 7.65 (d, 1 H), 7.45 (dd, 1 H), 7.23 (d, 1 H), 7.12 (d, 1 H), 7.07 (d, 1 H), 6.99 (dd, 1 H), 6.11 (d, 1 H), 5.04/4.84 (m+m, 2 H), 4.81 (t, 1 H), 4.36/3.99 (m+m, 2 H), 4.35/3.94 (d+d, 2 H), 4.14/3.68 (d+d, 2 H), 3.88 (q, 2 H), 3.41/3.14 (m+m, 2 H), 3.36/2.85 (m+m, 2 H), 3.12/3.08 (dd+dd, 2 H), 2.74 (s, 3 H), 2.31 (s, 3 H), 0.98 (t, 3 H)

20

**STEP 3 : Preparation of [4,32-dimethyl-28,28-dioxo-22,27-dioxa-19,28 $\lambda^6$ -dithia-1,14,15,16-tetraazahexacyclo[21.5.3.1<sup>3,7</sup>.1<sup>9,13</sup>.0<sup>12,16</sup>.0<sup>26,30</sup>]tritriaconta-3(33),4,6,9(32),10,12,14,23,25,30-decaen-8-yl]acetic acid**

25 Using General Procedure 12 starting from ethyl [4,32-dimethyl-28,28-dioxo-22,27-dioxa-19,28 $\lambda^6$ -dithia-1,14,15,16-tetraazahexacyclo[21.5.3.1<sup>3,7</sup>.1<sup>9,13</sup>.0<sup>12,16</sup>.0<sup>26,30</sup>]tritriaconta-3(33),4,6,9(32),10,12,14,23,25,30-decaen-8-yl]acetate E1 (1 eq.) or E2 (1 eq.) as reactants, the title compounds (77% - 74% yields respectively) were obtained.

30 **Example 63a (E1)**

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HRMS calculated for  $C_{29}H_{30}N_4O_6S_2$ : 594.1607;  $[M+H]^+$  found: 595.1686 ( $\delta = 1.1$  ppm)

**Example 63b (E2)**

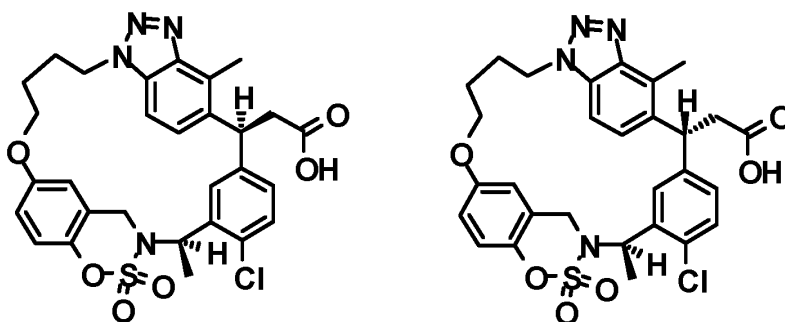
HRMS calculated for  $C_{29}H_{30}N_4O_6S_2$ : 594.1607;  $[M+H]^+$  found: 595.1681 ( $\delta = 0.2$  ppm)

5  $^1H$ -NMR (500 MHz, DMSO- $d_6$ )  $\delta$  ppm: 12.08 (br., 1 H), 7.72 (d, 1 H), 7.62 (d, 1 H), 7.44 (dd, 1 H), 7.23 (d, 1 H), 7.11 (d, 1 H), 7.04 (d, 1 H), 6.98 (dd, 1 H), 6.11 (d, 1 H), 5.03/4.84 (m+m, 2 H), 4.78 (t, 1 H), 4.33/3.96 (d+d, 2 H), 4.33/3.97 (m+m, 2 H), 4.13/3.71 (d+d, 2 H), 3.4/3.16 (m+m, 2 H), 3.33/2.85 (m+m, 2 H), 3 (d, 2 H), 2.73 (s, 3 H), 2.31 (s, 3 H)

10  $^{13}C$ -NMR (125 MHz, DMSO- $d_6$ )  $\delta$  ppm: 131.4, 131.2, 129.3, 127, 119.2, 114.9, 114.3, 108.2, 71.5, 51.8, 48.4, 47.2, 41.6, 41.2, 31.3, 28.8, 18.3, 13.3

**EXAMPLE 64** : [(2*R*,8*S*)-4-chloro-2,31-dimethyl-27,27-dioxo-21,26-dioxa-27 $\lambda^6$ -thia-1,14,15,16-tetraazahexacyclo[20.5.3.1<sup>3,7</sup>.1<sup>9,13</sup>.0<sup>12,16</sup>.0<sup>25,29</sup>]dotriacont-3(32),4,6,9(31),10,12,14,22,24,29-decaen-8-yl]acetic acid and

15 [(2*R*,8*R*)-4-chloro-2,31-dimethyl-27,27-dioxo-21,26-dioxa-27 $\lambda^6$ -thia-1,14,15,16-tetraazahexacyclo[20.5.3.1<sup>3,7</sup>.1<sup>9,13</sup>.0<sup>12,16</sup>.0<sup>25,29</sup>]dotriacont-3(32),4,6,9(31),10,12,14,22,24,29-decaen-8-yl]acetic acid



20

**STEP B1** : Preparation of (1*S*)-1-[2-chloro-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]ethan-1-ol

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Using General Procedure 3 starting from (1*S*)-1-(5-bromo-2-chlorophenyl)ethan-1-ol (1 eq., 7.8 g., 33.1 mmol) as a reactant, gave the title compound (7.1 g, 76% yield).

<sup>1</sup>H-NMR (400 MHz, DMSO-d<sub>6</sub>) δ ppm: 7.98 (d, 1 H), 7.5 (dd, 1 H), 7.38 (dd, 1 H), 5.4 (d, 1 H), 5.01 (m, 1 H), 1.3 (d+s, 15 H)

5

**STEP 1 : Preparation of ethyl 3-{1-[4-(benzyloxy)butyl]-4-methyl-1*H*-benzotriazol-5-yl}-3-{4-chloro-3-[(1*S*)-1-hydroxyethyl]phenyl}propanoate**

Using General Procedure 6 starting from ethyl (2*E*)-3-{1-[4-(benzyloxy)butyl]-4-methyl-1*H*-benzotriazol-5-yl}prop-2-enoate (1 eq.) and (1*S*)-1-[2-chloro-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]ethan-1-ol (2 eq.) as reactants, the title compound (87% yield) was obtained.

<sup>1</sup>H-NMR (400 MHz, DMSO-d<sub>6</sub>) δ ppm: 7.61/7.47 (2dd, 2 H), 7.56/7.33-7.19 (s+m, 8 H), 5.32/5.3 (2d, 1 H), 4.94 (m, 1 H), 4.86 (m, 1 H), 4.66 (2t, 2 H), 4.4 (s, 2 H), 3.93 (q, 2 H), 3.42 (t, 2 H), 3.17 (m, 2 H), 2.77/2.76 (2s, 3 H), 1.94 (quint, 2 H), 1.5 (quint, 2 H), 1.27/1.24 (2d, 3 H), 1 (t, 3 H)

15

**STEP 2 : Preparation of ethyl 3-{1-[4-(benzyloxy)butyl]-4-methyl-1*H*-benzotriazol-5-yl}-3-{3-[(1*R*)-1-[6-(benzyloxy)-2,2-dioxo-2*H*-1,2λ<sup>6</sup>,3-benzoxathiazin-3(4*H*)-yl]ethyl}-4-chlorophenyl}propanoate**

20

Using General Procedure 7 starting from ethyl 3-{1-[4-(benzyloxy)butyl]-4-methyl-1*H*-benzotriazol-5-yl}-3-{4-chloro-3-[(1*S*)-1-hydroxyethyl]phenyl}propanoate (1 eq.) and 6-(benzyloxy)-3,4-dihydro-2*H*-1,2λ<sup>6</sup>,3-benzoxathiazine-2,2-dione (1.1 eq.) as reactants, the title compound (82% yield) was obtained.

25

<sup>1</sup>H-NMR (400 MHz, DMSO-d<sub>6</sub>) δ ppm: 0.93 - 1.01 (m, 3 H) 1.40 - 1.54 (m, 5 H) 1.86 - 1.98 (m, 2 H) 2.77 (s, 3 H) 3.19 - 3.26 (m, 2 H) 3.36 - 3.45 (m, 2 H) 3.85 - 3.98 (m, 2 H) 4.36 - 4.41 (m, 2 H) 4.43 - 4.60 (m, 2 H) 4.60 - 4.70 (m, 2 H) 4.84 - 4.95 (m, 1 H) 5.03 - 5.13 (m, 2 H) 5.35 - 5.43 (m, 1 H) 6.81 - 6.94 (m, 1 H) 6.98 - 7.07 (m, 1 H) 7.17 - 7.31 (m, 5 H) 7.36 (s, 1 H) 7.37 - 7.47 (m, 5 H) 7.51 - 7.57 (m, 1 H) 7.62 (d, J=8.56 Hz, 1 H)

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**STEP 3 : Preparation of ethyl 3-{4-chloro-3-[(1*R*)-1-(6-hydroxy-2,2-dioxo-2*H*-1,2λ<sup>6</sup>,3-benzoxathiazin-3(4*H*)-yl)ethyl]phenyl}-3-[1-(4-hydroxybutyl)-4-methyl-1*H*-benzotriazol-5-yl]propanoate**

5

Using General Procedure 8 starting from ethyl 3-{1-[4-(benzyloxy)butyl]-4-methyl-1*H*-benzotriazol-5-yl}-3-(3-{(1*R*)-1-[6-(benzyloxy)-2,2-dioxo-2*H*-1,2λ<sup>6</sup>,3-benzoxathiazin-3(4*H*)-yl]ethyl}-4-chlorophenyl)propanoate (1 eq.) as a reactant, the title compound (48% yield) was obtained.

10 **<sup>1</sup>H-NMR** (400 MHz, DMSO-d<sub>6</sub>) δ ppm: 9.6 (s, 1 H), 7.65 (m, 2 H), 7.6 (d, 1 H), 7.35 (d, 1 H), 7.2 (dd, 1 H), 6.9 (d, 1 H), 6.7 (dd, 1 H), 6.6 (d, 1 H), 5.4 (m, 1 H), 4.9 (m, 1 H), 4.65 (t, 2 H), 4.45 (m, 3 H), 3.95 (q, 2 H), 3.4 (q, 2 H), 3.25 (d, 2 H), 2.8 (s, 3 H), 1.9 (m, 2 H), 1.5 (m, 3 H), 1.4 (m, 2 H), 1 (2t, 3 H)

15 **STEP 4 : Preparation of ethyl 3-[1-(4-bromobutyl)-4-methyl-1*H*-benzotriazol-5-yl]-3-{4-chloro-3-[(1*R*)-1-(6-hydroxy-2,2-dioxo-2*H*-1,2λ<sup>6</sup>,3-benzoxathiazin-3(4*H*)-yl)ethyl]phenyl]propanoate**

Using General Procedure 9 starting from ethyl 3-{4-chloro-3-[(1*R*)-1-(6-hydroxy-2,2-dioxo-2*H*-1,2λ<sup>6</sup>,3-benzoxathiazin-3(4*H*)-yl)ethyl]phenyl}-3-[1-(4-hydroxybutyl)-4-methyl-1*H*-benzotriazol-5-yl]propanoate (1 eq.) as a reactant, the title compound (yellow oil, 70% yield) was obtained.

20 **<sup>1</sup>H-NMR** (400 MHz, DMSO-d<sub>6</sub>) δ ppm: 9.63/9.62 (2m, 1 H), 7.67 (d, 1 H), 7.66/7.58 (dd, 2 H), 7.36 (d, 1 H), 7.25 (dd, 1 H), 6.9 (d, 1 H), 6.72 (m, 1 H), 6.62/6.59 (d, 1 H), 5.37 (m, 1 H), 4.94-4.87 (m, 1 H), 4.7 (t, 2 H), 4.51-4.39 (m, 2 H), 3.94 (q, 2 H), 3.54 (q, 2 H), 3.25 (d, 2 H), 2.77 (s, 3 H), 2 (m, 2 H), 1.77 (m, 2 H), 1.46 (m, 3 H), 1 (t, 3 H)

**STEP 5 : Preparation of ethyl [(2*R*)-4-chloro-2,31-dimethyl-27,27-dioxo-21,26-dioxa-27λ<sup>6</sup>-thia-1,14,15,16-tetraazahexacyclo[20.5.3.1<sup>3,7</sup>.1<sup>9,13</sup>.0<sup>12,16</sup>.0<sup>25,29</sup>]dotriaconta-3(32),4,6,9(31),10,12,14,22,24,29-decaen-8-yl]acetate**

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Using General Procedure 11 starting from ethyl 3-[1-(4-bromobutyl)-4-methyl-1*H*-benzotriazol-5-yl]-3-{4-chloro-3-[(1*R*)-1-(6-hydroxy-2,2-dioxo-2*H*-1,2λ<sup>6</sup>,3-benzoxathiazin-3(4*H*)-yl)ethyl] phenyl} propanoate (1 eq.) as a reactant, the title compound (white solid, 98% yield) was obtained.

<sup>1</sup>H-NMR (400 MHz, DMSO-d<sub>6</sub>) δ ppm: 0.96 - 1.08 (m, 5 H) 1.14 (d, J=6.85 Hz, 2 H) 1.29 (d, J=6.97 Hz, 4 H) 1.55 - 1.77 (m, 2 H) 1.77 - 1.90 (m, 1 H) 1.92 - 2.27 (m, 3 H) 2.61 - 2.86 (m, 5 H) 2.98 - 3.20 (m, 2 H) 3.34 - 3.53 (m, 4 H) 3.59 - 3.80 (m, 2 H) 3.86 - 4.03 (m, 3 H) 4.03 - 4.17 (m, 2 H) 4.66 - 4.80 (m, 3 H) 4.86 (t, J=7.95 Hz, 1 H) 4.95 (t, J=7.76 Hz, 1 H) 5.28 - 5.47 (m, 2 H) 5.72 (d, J=2.81 Hz, 1 H) 5.85 (br. s., 1 H) 6.66 - 6.80 (m, 2 H) 6.87 - 6.98 (m, 2 H) 7.15 (d, J=8.80 Hz, 1 H) 7.31 (d, J=1.96 Hz, 1 H) 7.48 (d, J=8.19 Hz, 1 H) 7.57 - 7.63 (m, 2 H) 7.71 (d, J=8.68 Hz, 1 H) 7.78 (d, J=8.68 Hz, 1 H) 7.91 (d, J=8.80 Hz, 1 H)

#### STEP 6 : Preparation of EXAMPLE 64

Using General Procedure 12 starting from ethyl [(2*R*)-4-chloro-2,31-dimethyl-27,27-dioxo-21,26-dioxa-27λ<sup>6</sup>-thia-1,14,15,16-tetraazahexacyclo[20.5.3.1<sup>3,7</sup>.1<sup>9,13</sup>.0<sup>12,16</sup>.0<sup>25,29</sup>]dotriaconta-3(32),4,6,9(31),10,12,14,22,24,29-decaen-8-yl]acetate (1 eq.) as a reactant, the title compound (white solid, quant.) was obtained.

The diastereo-pure products were obtained by chromatographic separation on chiral column.

#### Example 64a (2*R*,8*S*)

HRMS calculated for C<sub>29</sub>H<sub>29</sub>ClN<sub>4</sub>O<sub>6</sub>S: 596.1496; [M+H]<sup>+</sup> found: 597.1572 (δ=0.5 ppm)

<sup>1</sup>H-NMR (400 MHz, DMSO-d<sub>6</sub>) δ ppm: 12.16 (m, 1 H), 7.9 (d, 1 H), 7.78 (d, 1 H), 7.61 (dd, 1 H), 7.49 (d, 1 H), 7.27 (d, 1 H), 6.94 (d, 1 H), 6.75 (dd, 1 H), 5.69 (d, 1 H), 5.4 (m, 1 H), 4.83 (m, 1 H), 4.82-4.68 (m, 2 H), 4.1/3.38 (dd, 2 H), 3.67/3.47 (2m, 2 H), 3.24/3.05 (2dd, 2 H), 2.66 (s, 3 H), 2.18/2.1 (2m, 2 H), 1.86/1.74 (2m, 2 H), 1.28 (d, 3 H)

#### Example 64b (2*R*,8*R*)

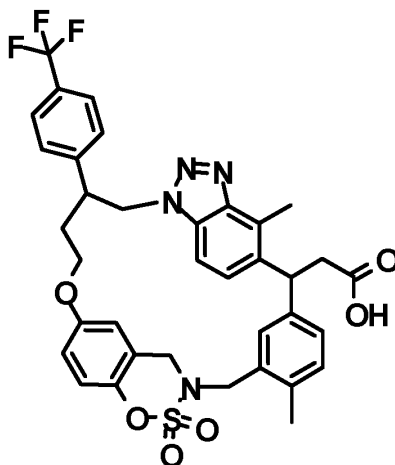
HRMS calculated for C<sub>29</sub>H<sub>29</sub>ClN<sub>4</sub>O<sub>6</sub>S: 596.1496; [M+H]<sup>+</sup> found: 597.1573 (δ=0.7 ppm)

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<sup>1</sup>H-NMR (400 MHz, DMSO-d<sub>6</sub>) δ ppm: 12.33 (m, 1 H), 7.71 (d, 1 H), 7.6/6.9 (2s, 3 H), 7.11 (d, 1 H), 6.92 (d, 1 H), 6.73 (dd, 1 H), 5.86 (d, 1 H), 5.36 (q, 1 H), 4.93 (m, 1 H), 4.76 (m, 2 H), 4.1/3.49 (dd, 2 H), 3.76/3.65 (2m, 2 H), 3.28/2.91 (2dd, 2 H), 2.66 (s, 3 H), 2.21/2.04 (2m, 2 H), 1.66/1.32 (2m, 2 H), 1.14 (d, 3 H)

5

**EXAMPLE 65** : {4,31-Dimethyl-27,27-dioxo-18-[4-(trifluoromethyl)phenyl]-21,26-dioxo-27λ<sup>6</sup>-thia-1,14,15,16-tetraazahexacyclo[20.5.3.1<sup>3,7</sup>.1<sup>9,13</sup>.0<sup>12,16</sup>.0<sup>25,29</sup>]dotriaconta-3(32),4,6,9(31),10,12,14,22,24,29-decaen-8-yl}acetic acid



10 **STEP 1** : Preparation of ethyl 3-(3-{[6-(benzyloxy)-2,2-dioxo-2*H*-1,2λ<sup>6</sup>,3-benzoxathiazin-3(4*H*)-yl]methyl}-4-methylphenyl)-3-[4-({4-hydroxy-2-[4-(trifluoromethyl)phenyl]butyl}amino)-2-methyl-3-nitrophenyl]propanoate

Ethyl 3-(3-{[6-(benzyloxy)-2,2-dioxo-2*H*-1,2λ<sup>6</sup>,3-benzoxathiazin-3(4*H*)-yl]methyl}-4-methylphenyl)-3-(4-fluoro-2-methyl-3-nitrophenyl)propanoate (1 eq., 2 g, 3.1 mmol) and 4-amino-3-[4-(trifluoromethyl)phenyl]butan-1-ol (1.5 eq., 1.078 g, 4.622 mmol) were dissolved in N,N-dimethylacetamide (5 mL). DIPEA (1.85 eq., 1 mL, 5.741 mmol) was added and the mixture was stirred under N<sub>2</sub> atmosphere at 100 °C overnight. Excess of 4-amino-3-[4-(trifluoromethyl)phenyl]butan-1-ol (0.25 g, 1.072 mmol) was added followed by addition of

20 DIPEA (0.3 mL, 1.72 mmol), and the mixture was stirred at 100°C for additional 24 h. After

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cooling, pouring on chilled brine and extraction with DCM, the collected organic phases were dried over Na<sub>2</sub>SO<sub>4</sub> and evaporated to Celite. The crude product was purified by normal phase silica gel chromatography using DCM-MeOH (100:0 to 95.2:4.8) eluents resulted in 2.334 g (88% yield) of the title compound after drying in high vacuo at RT.

5 <sup>1</sup>H-NMR (500 MHz, DMSO-d<sub>6</sub>) δ ppm: 7.63/7.62 (d/d, 2 H), 7.43 (d, 2 H), 7.41 (d/d, 2 H), 7.39 (t, 2 H), 7.34 (t, 1 H), 7.33 (d, 1 H), 7.16 (db, 1 H), 7.15 (d, 1 H), 7.14 (d, 1 H), 7.11 (dd, 1 H), 7.07 (dd, 1 H), 6.99/6.98 (d/d, 1 H), 6.75 (d, 1 H), 5.62 (t, 1 H), 5.09 (s, 2 H), 4.53 (t, 1 H), 4.46/4.42 (d+d, 2 H), 4.45 (t, 1 H), 4.24/4.23/4.19/4.19 (d+d/d+d, 2 H), 3.97/3.95 (q/q, 2 H), 3.39/3.27 (m+m, 2 H), 3.28/3.27/3.18/3.16 (m+m/m+m, 2 H), 3.13 (m, 1 H), 3.05/3.04/3.01/3.00 (dd+dd/dd+dd, 2 H), 2.22/2.21 (s/s, 3 H), 2.11 (s, 3 H), 1.88/1.7 (m+m, 2 H), 1.04/1.03 (t/t, 3 H)

15 **STEP 2 : Preparation of ethyl 3-[3-amino-4-({4-hydroxy-2-[4-(trifluoromethyl)phenyl]butyl}amino)-2-methylphenyl]-3-(3-{{6-(benzyloxy)-2,2-dioxo-2H-1,2λ<sup>6</sup>,3-benzoxathiazin-3(4H)-yl}methyl}-4-methylphenyl)propanoate**

To a solution of ethyl 3-(3-{{6-(benzyloxy)-2,2-dioxo-2H-1,2λ<sup>6</sup>,3-benzoxathiazin-3(4H)-yl}methyl}-4-methylphenyl)-3-[4-({4-hydroxy-2-[4-(trifluoromethyl)phenyl]butyl}amino)-2-methyl-3-nitrophenyl]propanoate (1 eq., 2.327 g, 2.7P mmol) in 1,2-dichloroethane (7 mL) and IPA (7 mL) Raney-nickel catalyst (0.65 g, 7.6 mmol) was added. Hydrazine hydrate (0.8109 g, 0.7858 mL, 8.100 mmol) was added dropwise over a period of 60 minutes (exothermic reaction!) and the reaction mixture was stirred at RT for further 30 min. The reaction mixture was filtered through a pad of Celite, the Celite was washed with DCM (3x15 mL) and THF (2x15 mL). The filtrate was evaporated to yield 2.267 g (quant.) of the title compound as a light yellow foamy material.

<sup>1</sup>H-NMR (500 MHz, DMSO-d<sub>6</sub>) δ ppm: 7.63 (m, 2 H), 7.48-7.3 (m, 5 H), 7.46 (m, 2 H), 7.14 (d, 1 H), 7.09 (d, 1 H), 7.07 (dd, 1 H), 7.06 (d, 1 H), 7.02/7.01 (dd, 1 H), 6.98 (d, 1 H), 6.35 (d, 1 H), 5.1 (s, 2 H), 4.51 (t, 1 H), 4.43 (t, 1 H), 4.42 (s, 2 H), 4.32 (t, 1 H), 4.21/4.14 (d+d, 2 H),

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4.12 (s, 2 H), 3.96/3.93 (m+m, 2 H), 3.48 (d, 1 H), 3.29/3.19 (m+m, 2 H), 3.23/3.16 (m+m, 2 H), 3.15 (m, 1 H), 2.9 (d, 2 H), 2.2 (s, 3 H), 1.98-1.72 (m+m, 2 H), 1.94 (s, 3 H), 1.05 (t, 3 H)

**STEP 3 : Preparation of ethyl 3-(3-{[6-(benzyloxy)-2,2-dioxo-2*H*-1,2λ<sup>6</sup>,3-benzoxathiazin-3(4*H*)-yl]methyl}-4-methylphenyl)-3-(1-{4-hydroxy-2-[4-(trifluoromethyl)phenyl]butyl}-4-methyl-1*H*-benzotriazol-5-yl)propanoate**

Ethyl 3-[3-amino-4-(4-hydroxy-2-[4-(trifluoromethyl)phenyl]butyl)amino)-2-methylphenyl]-3-(3-{[6-(benzyloxy)-2,2-dioxo-2*H*-1,2λ<sup>6</sup>,3-benzoxathiazin-3(4*H*)-yl]methyl}-4-methylphenyl) propanoate (1 eq., 2.24 g, 2.69 mmol) was dissolved in a mixture of THF (15 mL) and AcOH (1.5 mL). To this clear solution 3-methylbutyl nitrite (3 eq., 0.946 g, 1.09 mL, 8.08 mmol) was added dropwise at 0°C and the mixture was stirred at RT for 3h. The mixture was poured on sat. NaHCO<sub>3</sub> solution and extracted with EtOAc. The aq. layer was washed with further EtOAc portions, the combined organic layer was dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and evaporated under reduced pressure. The crude product was purified by preparative HPLC on reversed-phase C18 column using aq. NH<sub>4</sub>HCO<sub>3</sub>-MeCN (100:0 to 30:70) as an eluent to give 0.80 g (40% yield) of the title compound as a light yellow foamy material.

<sup>1</sup>H-NMR (500 MHz, DMSO-d<sub>6</sub>) δ ppm: 7.53 (d, 2 H), 7.47 (d, 1 H), 7.46 (m, 2 H), 7.44/7.43 (d/d, 1 H), 7.41 (m, 2 H), 7.4 (m, 2 H), 7.34 (tm, 1 H), 7.22 (brs., 1 H), 7.17/7.11 (dd/m, 1 H), 7.14 (d, 1 H), 7.11 (m, 1 H), 7.07 (dd, 1 H), 6.96/6.95 (d/d, 1 H), 5.11/5.08 (d+d, 2 H), 4.89 (m, 2 H), 4.8 (t, 1 H), 4.48/4.47 (t/t, 1 H), 4.44 (m, 2 H), 4.21 (m, 2 H), 3.92/3.89 (q/q, 2 H), 3.58 (m, 1 H), 3.27/3.14 (m+m, 2 H), 3.14 (m, 2 H), 2.7 (s, 3 H), 2.21 (s, 3 H), 1.82 (m, 2 H), 0.96/0.92 (t/t, 3 H)

**STEP 4 : Preparation of ethyl 3-{3-[(6-hydroxy-2,2-dioxo-2*H*-1,2λ<sup>6</sup>,3-benzoxathiazin-3(4*H*)-yl)methyl]-4-methylphenyl}-3-(1-{4-hydroxy-2-[4-(trifluoromethyl)phenyl]butyl}-4-methyl-1*H*-benzotriazol-5-yl)propanoate**

Using General Procedure 8 starting from ethyl 3-(3-{[6-(benzyloxy)-2,2-dioxo-2*H*-1,2λ<sup>6</sup>,3-benzoxathiazin-3(4*H*)-yl]methyl}-4-methylphenyl)-3-(1-{4-hydroxy-2-[4-(trifluoromethyl)

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phenyl]butyl}-4-methyl-1*H*-benzotriazol-5-yl)propanoate (1 eq.) as a reactant, the title compound (white foamy material, 96% yield) was obtained.

**<sup>1</sup>H-NMR** (500 MHz, DMSO-d<sub>6</sub>) δ ppm: 9.71 (s, 1 H), 7.55 (d, 2 H), 7.5/7.48 (d/d, 1 H), 7.45 (d, 1 H), 7.43 (d, 2 H), 7.21 (brs., 1 H), 7.17/7.11 (d/d, 1 H), 7.12 (m, 1 H), 7 (d, 1 H), 6.79 (dd, 1 H), 6.61/6.6 (d/d, 1 H), 4.92 (m, 2 H), 4.79 (t, 1 H), 4.38 (s, 2 H), 4.21/4.17 (d+d, 2 H), 3.91 (m, 2 H), 3.6 (m, 1 H), 3.28/3.15 (m+m, 2 H), 3.14 (m, 2 H), 2.7/2.69 (s/s, 3 H), 2.22 (s, 3 H), 1.83 (m, 2 H), 0.97/0.94 (t/t, 3 H)

**STEP 5 : Preparation of ethyl 3-(1-{4-chloro-2-[4-(trifluoromethyl)phenyl]butyl}-4-methyl-1*H*-benzotriazol-5-yl)-3-{3-[(6-hydroxy-2,2-dioxo-2*H*-1,2λ<sup>6</sup>,3-benzoxathiazin-3(4*H*)-yl)methyl]-4-methylphenyl}propanoate**

Using General Procedure 10 starting from ethyl 3-{3-[(6-hydroxy-2,2-dioxo-2*H*-1,2λ<sup>6</sup>,3-benzoxathiazin-3(4*H*)-yl)methyl]-4-methylphenyl}-3-(1-{4-hydroxy-2-[4-(trifluoromethyl)phenyl]butyl}-4-methyl-1*H*-benzotriazol-5-yl)propanoate (1 eq.) as a reactant, the title compound (yellow solid foam, quant.) was obtained. The product was used in the next step without further purification.

**<sup>1</sup>H-NMR** (500 MHz, DMSO-d<sub>6</sub>) δ ppm: 9.72 (br., 1 H), 7.58 (d, 2 H), 7.5/7.49 (d/d, 1 H), 7.47/7.45 (d/d, 1 H), 7.4 (d, 2 H), 7.21 (brs., 1 H), 7.17/7.11 (d/d, 1 H), 7.12 (m, 1 H), 6.99 (d, 1 H), 6.79 (dd, 1 H), 6.61 (brs., 1 H), 4.97 (m, 2 H), 4.79 (t, 1 H), 4.38 (s, 2 H), 4.21/4.17 (d+d, 2 H), 3.91 (m, 2 H), 3.66 (m, 1 H), 3.53/3.31 (m+m, 2 H), 3.14 (m, 2 H), 2.69 (s/s, 3 H), 2.24/2.12 (m+m, 2 H), 2.22 (s, 3 H), 0.97/0.93 (t/t, 3 H)

**STEP 6 : Preparation of ethyl {4,31-dimethyl-27,27-dioxo-18-[4-(trifluoromethyl)phenyl]-21,26-dioxo-27λ<sup>6</sup>-thia-1,14,15,16-tetraazahexacyclo[20.5.3.1<sup>3,7</sup>.1<sup>9,13</sup>.0<sup>12,16</sup>.0<sup>25,29</sup>]dotriacont-3(32),4,6,9(31),10,12,14,22,24,29-decaen-8-yl}acetate**

Ethyl 3-(1-{4-chloro-2-[4-(trifluoromethyl)phenyl]butyl}-4-methyl-1*H*-benzotriazol-5-yl)-3-{3-[(6-hydroxy-2,2-dioxo-2*H*-1,2λ<sup>6</sup>,3-benzoxathiazin-3(4*H*)-yl)methyl]-4-

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methylphenyl} propanoate (1 eq., 0.55 g, 0.71 mmol) was dissolved in N,N-dimethylacetamide (5 mL). Cs<sub>2</sub>CO<sub>3</sub> (1.7 eq., 0.50 g, 1.5 mmol) was added and the mixture was stirred at 120 °C for 3h. After completion of the reaction the mixture was filtered through a pad of Celite, which was washed with DCM. The mother liquor was evaporated and the crude product was purified by  
 5 reversed-phase C18 column chromatography using aq. NH<sub>4</sub>HCO<sub>3</sub>-MeCN (100:0 to 0:100), resulted in 0.23 g (44% yield) of the desired compound as a yellowish foamy material.

**<sup>1</sup>H-NMR** (500 MHz, DMSO-d<sub>6</sub>, mixture of diastereomers) δ ppm: 7.87/7.84 (d/d, 1 H), 7.8/7.78 (s/d, 2 H), 7.8/7.67 (s/d, 2 H), 7.58/7.5 (d/d, 1 H), 7.51/7.49 (dd/dd, 1 H), 7.31/7.29 (d/d, 1 H), 7 (d, 1 H), 6.79/6.77 (dd/dd, 1 H), 6.61/6.55 (d/d, 1 H), 6.02/5.82 (d/d, 1 H), 5.16/5.04/4.86/4.77  
 10 (dd/dd+dd/dd, 2 H), 4.8 (t, 1 H), 4.22/4.15/3.97/3.87 (d/d+d/d, 2 H), 4.08/4.04/3.85/3.82 (d/d+d/d, 2 H), 3.93/3.92 (q/q, 2 H), 3.78/3.6 (m/m, 1 H), 3.61/3.53/3.53/3.06 (m/m+m/m, 2 H), 3.22-3.03 (m, 2 H), 2.64/2.62 (s/s, 3 H), 2.35-2 (m, 2 H), 2.34/2.33 (s/s, 3 H), 1.02/1.01 (t/t, 3 H)

#### 15 STEP 7 : Preparation of EXAMPLE 65

Using General Procedure 12 starting from ethyl {4,31-dimethyl-27,27-dioxo-18-[4-(trifluoromethyl)phenyl]-21,26-dioxa-27λ<sup>6</sup>-thia-1,14,15,16-tetraazahexacyclo  
 [20.5.3.1<sup>3,7</sup>.1<sup>9,13</sup>.0<sup>12,16</sup>.0<sup>25,29</sup>]dotriaconta-3(32),4,6,9(31),10,12,14,22,24,29-decaen-8-yl} acetate  
 20 (1 eq.) as a reactant, the title compound (white solid, 29% yield) was obtained.

**HRMS** calculated for C<sub>36</sub>H<sub>33</sub>F<sub>3</sub>N<sub>4</sub>O<sub>6</sub>S: 706.2073; [M+H]<sup>+</sup> found: 707.2142 (δ = -0.5 ppm)

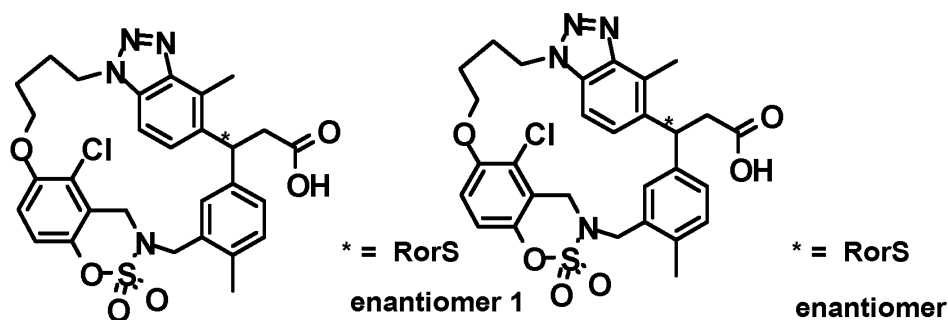
**<sup>1</sup>H-NMR** (500 MHz, DMSO-d<sub>6</sub>, mixture of diastereomers) δ ppm: 12.13 (br., 1 H), 7.86/7.84 (d/d, 1 H), 7.8/7.68 (s/d, 2 H), 7.8/7.78 (s/d, 2 H), 7.56/7.5 (d/d, 1 H), 7.52/7.5 (dd/dd, 1 H), 7.31/7.3 (d/d, 1 H), 6.99 (d, 1 H), 6.79/6.77 (dd/dd, 1 H), 6.59/6.53 (d/d, 1 H), 6/5.81 (d/d, 1  
 25 H), 5.15/5.04/4.85/4.77 (dd/dd+dd/dd, 2 H), 4.78 (t, 1 H), 4.22/4.14/3.98/3.87 (d/d+d/d, 2 H), 4.07/4.04/3.86/3.82 (d/d+d/d, 2 H), 3.78/3.63 (m/m, 1 H), 3.67-3.02 (m, 2 H), 3.06/2.99 (m+m, 2 H), 2.63/2.62 (s/s, 3 H), 2.38-2.02 (m, 2 H), 2.34/2.33 (s/s, 3 H)

**<sup>13</sup>C-NMR** (125 MHz, DMSO-d<sub>6</sub>) δ ppm: 173.2, 131.4/131.3, 131.1, 129.5/129.2, 128.8, 127.6/127.4, 126.1, 119.6/119.4, 117.7/117.3, 111.7/111.3, 108.3/108, 66.5/66.3, 54/52.5,  
 30 51.9, 48.8/48.7, 43.7/41.2, 41.9/41.8, 40.9, 34.2/32.7, 18.5/18.4, 13.5/13.4

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**EXAMPLE 66 :** [30-Chloro-4,31-dimethyl-27,27-dioxo-21,26-dioxo-27 $\lambda^6$ -thia-1,14,15,16-tetraazahexacyclo[20.5.3.1<sup>3,7</sup>.1<sup>9,13</sup>.0<sup>12,16</sup>.0<sup>25,29</sup>]dotriaconta-3(32),4,6,9(31),10,12,14,22,24,29-decaen-8-yl]acetic acid

5



**STEP 1 :** Preparation of 6-(benzyloxy)-3-[(5-bromo-2-methylphenyl)methyl]-5-chloro-3,4-dihydro-2H-1,2 $\lambda^6$ ,3-benzoxathiazine-2,2-dione

10

6-(Benzyloxy)-3-[(5-bromo-2-methylphenyl)methyl]-3,4-dihydro-2H-1,2 $\lambda^6$ ,3-benzoxathiazine-2,2-dione (1 eq., 2 g, 4.2 mmol) was dissolved in nitromethane (40 mL), then Oxone ® (3 eq., 7.78 g, 12.7 mmol) and potassium chloride (1.8 eq., 5.66 g, 7.5921 mmol) were added. The reaction mixture was stirred at 60°C for 2 days. After concentration under reduced pressure, the residue was dissolved in DCM and the solution was washed with water. The organic phase was dried over MgSO<sub>4</sub>, filtered and concentrated under reduced pressure to give 2.078 g of the crude product, which was purified via flash chromatography using heptane-EtOAc as eluents to give the title compound (1.404 g, 2.759 mmol, 65% yield) as a yellowish oil.

20

**<sup>1</sup>H-NMR** (500 MHz, DMSO-d<sub>6</sub>)  $\delta$  ppm: 7.51-7.32 (m, 5 H), 7.5 (d, 1 H), 7.47 (dd, 1 H), 7.34 (d, 1 H), 7.22 (d, 1 H), 7.21 (d, 1 H), 5.25 (s, 2 H), 4.59 (s, 2 H), 4.36 (s, 2 H), 2.26 (s, 3 H)



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**STEP 2 : Preparation of 6-(benzyloxy)-5-chloro-3-{[2-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]methyl}-3,4-dihydro-2*H*-1,2λ<sup>6</sup>,3-benzoxathiazine-2,2-dione**

5 Using General Procedure 3 starting from 6-(benzyloxy)-3-[(5-bromo-2-methylphenyl)methyl]-5-chloro-3,4-dihydro-2*H*-1,2λ<sup>6</sup>,3-benzoxathiazine-2,2-dione (1 eq., 1.40 g, 2.75 mmol) as a reactant, the title compound (1.33 g, 87% yield) was obtained.

<sup>1</sup>H-NMR (500 MHz, DMSO-d<sub>6</sub>) δ ppm: 7.58 (dd, 1 H), 7.51 (d, 1 H), 7.49-7.33 (m, 5 H), 7.35 (s, 1 H), 7.28 (d, 1 H), 7.22 (d, 1 H), 5.25 (s, 2 H), 4.5 (s, 2 H), 4.34 (s, 2 H), 2.33 (s, 3 H), 1.28  
10 (s, 12 H)

**STEP 3 : Preparation of ethyl 3-{1-[4-(benzyloxy)butyl]-4-methyl-1*H*-benzotriazol-5-yl}-3-(3-{[6-(benzyloxy)-5-chloro-2,2-dioxo-2*H*-1,2λ<sup>6</sup>,3-benzoxathiazin-3(4*H*)-yl]methyl}-4-methylphenyl)propanoate**

15

Using General Procedure 6 starting from ethyl (2*E*)-3-{1-[4-(benzyloxy)butyl]-4-methyl-1*H*-benzotriazol-5-yl}prop-2-enoate (1 eq., 0.92 g, 2.34 mmol) and 6-(benzyloxy)-5-chloro-3-{[2-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]methyl}-3,4-dihydro-2*H*-1,2λ<sup>6</sup>,3-benzoxathiazine-2,2-dione (1 eq., 1.30 g, 2.34 mmol) as reactants, the title compound  
20 (638 mg, 33% yield) was obtained.

<sup>1</sup>H-NMR (500 MHz, DMSO-d<sub>6</sub>) δ ppm: 7.56 (d, 1 H), 7.51-7.21 (m, 10 H), 7.46 (d, 1 H), 7.33 (d, 1 H), 7.25 (m, 1 H), 7.24 (m, 1 H), 7.2 (d, 1 H), 7.16 (d, 1 H), 5.24 (s, 2 H), 4.84 (t, 1 H), 4.63 (t, 2 H), 4.39 (s, 2 H), 4.37 (s, 2 H), 4.26 (s, 2 H), 3.91 (q, 2 H), 3.38 (t, 2 H), 3.15 (d, 2 H), 2.76 (s, 3 H), 2.25 (s, 3 H), 1.91 (m, 2 H), 1.47 (m, 2 H), 0.97 (t, 3 H)

25

**STEP 4 : Preparation of ethyl 3-{3-[(5-chloro-6-hydroxy-2,2-dioxo-2*H*-1,2λ<sup>6</sup>,3-benzoxathiazin-3(4*H*)-yl)methyl]-4-methylphenyl}-3-[1-(4-hydroxybutyl)-4-methyl-1*H*-benzotriazol-5-yl]propanoate**

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Using General Procedure 8 starting from ethyl 3-{1-[4-(benzyloxy)butyl]-4-methyl-1*H*-benzotriazol-5-yl}-3-(3-{[6-(benzyloxy)-5-chloro-2,2-dioxo-2*H*-1,2λ<sup>6</sup>,3-benzoxathiazin-3(4*H*)-yl]methyl}-4-methylphenyl)propanoate (1 eq., 755 mg, 0.9169 mmol) as a reactant, the title compound (423 mg, 72% yield) was obtained.

- 5 <sup>1</sup>H-NMR (500 MHz, DMSO-d<sub>6</sub>) δ ppm: 10.5 (br., 1 H), 7.58 (d, 1 H), 7.48 (d, 1 H), 7.24 (m, 1 H), 7.24 (m, 1 H), 7.16 (d, 1 H), 7.04 (d, 1 H), 7.02 (d, 1 H), 4.84 (t, 1 H), 4.64 (t, 2 H), 4.43 (br., 1 H), 4.36 (s, 2 H), 4.26/4.22 (d+d, 2 H), 3.92 (q, 2 H), 3.38 (t, 2 H), 3.15 (d, 2 H), 2.76 (s, 3 H), 2.24 (s, 3 H), 1.9 (m, 2 H), 1.36 (m, 2 H), 0.99 (t, 3 H)

10 **STEP 5 : Preparation of ethyl 3-[1-(4-chlorobutyl)-4-methyl-1*H*-benzotriazol-5-yl]-3-{3-[(5-chloro-6-hydroxy-2,2-dioxo-2*H*-1,2λ<sup>6</sup>,3-benzoxathiazin-3(4*H*)-yl)methyl]-4-methylphenyl}propanoate**

- Using General Procedure 10 starting from ethyl 3-{3-[(5-chloro-6-hydroxy-2,2-dioxo-2*H*-1,2λ<sup>6</sup>,3-benzoxathiazin-3(4*H*)-yl)methyl]-4-methylphenyl}-3-[1-(4-hydroxybutyl)-4-methyl-1*H*-benzotriazol-5-yl]propanoate (1 eq., 420 mg, 0.6530 mmol) as a reactant, the title compound (444 mg, 99% yield) was obtained.

- <sup>1</sup>H-NMR (500 MHz, DMSO-d<sub>6</sub>) δ ppm: 10.52 (s, 1 H), 7.6 (d, 1 H), 7.49 (d, 1 H), 7.24 (dd, 1 H), 7.23 (d, 1 H), 7.16 (d, 1 H), 7.04 (d, 1 H), 7.02 (d, 1 H), 4.84 (t, 1 H), 4.68 (t, 2 H), 4.35 (s, 2 H), 4.25/4.22 (d+d, 2 H), 3.92 (q, 2 H), 3.64 (t, 2 H), 3.15 (d, 2 H), 2.75 (s, 3 H), 2.24 (s, 3 H), 1.99/1.68 (m+m, 4 H), 0.98 (t, 3 H)

25 **STEP 6 : Preparation of ethyl [30-chloro-4,31-dimethyl-27,27-dioxo-21,26-dioxa-27λ<sup>6</sup>-thia-1,14,15,16-tetraazahexacyclo[20.5.3.1<sup>3,7</sup>.1<sup>9,13</sup>.0<sup>12,16</sup>.0<sup>25,29</sup>]dotriacont-3(32),4,6,9(31),10,12,14,22,24,29-decaen-8-yl]acetate**

- Using General Procedure 11 starting from ethyl 3-[1-(4-chlorobutyl)-4-methyl-1*H*-benzotriazol-5-yl]-3-{3-[(5-chloro-6-hydroxy-2,2-dioxo-2*H*-1,2λ<sup>6</sup>,3-benzoxathiazin-3(4*H*)-yl)methyl]-4-methylphenyl}propanoate (1 eq., 432 mg, 0.6530 mmol) as a reactant, the title compound (372 mg, 91% yield) was obtained.

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**<sup>1</sup>H-NMR** (500 MHz, DMSO-d<sub>6</sub>) δ ppm: 7.55 (d, 1 H), 7.5 (dd, 1 H), 7.31 (d, 1 H), 7.31 (d, 1 H), 7.15 (d, 1 H), 7.06 (d, 1 H), 6.41 (d, 1 H), 4.78/4.73 (dm+dm, 2 H), 4.78 (t, 1 H), 4.12/4.01 (d+d, 2 H), 4.1/4.01 (m+m, 2 H), 4.05/3.98 (d+d, 2 H), 3.9 (m, 2 H), 3.23/3.01 (dd+dd, 2 H), 2.6 (s, 3 H), 2.33 (s, 3 H), 2.23/2.06 (m+m, 2 H), 1.67/1.53 (m+m, 2 H), 0.97 (t, 3 H)

5

#### STEP 7 : Preparation of EXAMPLE 66

Using General Procedure 12 starting from ethyl [30-chloro-4,31-dimethyl-27,27-dioxo-21,26-dioxa-27λ<sup>6</sup>-thia-1,14,15,16-tetraazahexacyclo[20.5.3.1<sup>3,7</sup>.1<sup>9,13</sup>.0<sup>12,16</sup>.0<sup>25,29</sup>]dotriaconta-

10 3(32),4,6,9(31),10,12,14,22,24,29-decaen-8-yl]acetate (1 eq., 370 mg, 0.5919 mmol) as a reactant, the title compound (221 mg, 63% yield) was obtained.

The enantiopure products were obtained by chromatographic separation on chiral column.

#### Example 66a (E1)

15 **HRMS** calculated for C<sub>29</sub>H<sub>29</sub>ClN<sub>4</sub>O<sub>6</sub>S: 596.1496; [M+H]<sup>+</sup> found: 597.1565 (δ = -0.7 ppm)

#### Example 66b (E2)

**HRMS** calculated for C<sub>29</sub>H<sub>29</sub>ClN<sub>4</sub>O<sub>6</sub>S: 596.1496; [M+H]<sup>+</sup> found: 597.1567 (δ = -0.4 ppm)

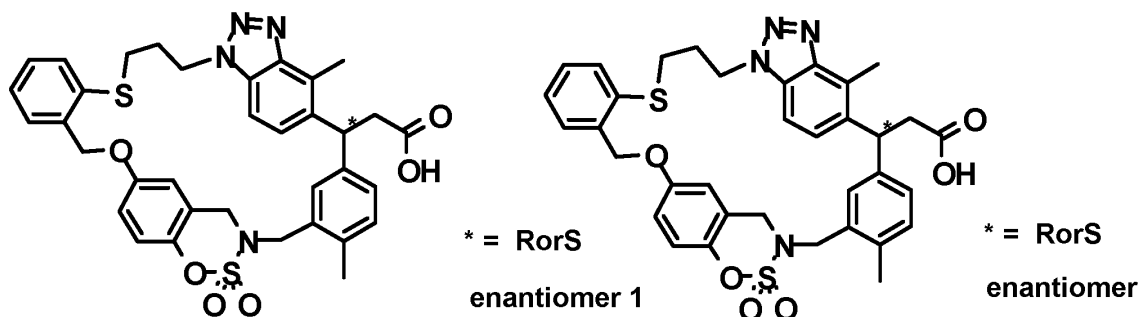
20 **<sup>1</sup>H-NMR** (500 MHz, DMSO-d<sub>6</sub>) δ ppm: 7.55 (d, 1 H), 7.51 (d, 1 H), 7.31 (d, 1 H), 7.29 (d, 1 H), 7.15 (d, 1 H), 7.05 (d, 1 H), 6.39 (s, 1 H), 4.79/4.71 (m+m, 2 H), 4.79/4.71 (d+d, 2 H), 4.76 (t, 1 H), 4.12/4.01 (d+d, 2 H), 4.09/4.01 (m+m, 2 H), 3.1/2.88 (dd+dd, 2 H), 2.6 (s, 3 H), 2.33 (s, 3 H), 2.24/2.07 (m+m, 2 H), 1.67/1.52 (m+m, 2 H)

**<sup>13</sup>C-NMR** (125 MHz, DMSO-d<sub>6</sub>) δ ppm: 131.4, 131.3, 128.4, 127, 118, 117.7, 108.5, 71.4, 52.7, 48, 48, 41.1, 41.1, 27.2, 26.5, 18.5, 13.3

25

**EXAMPLE 67** : [4,38-Dimethyl-34,34-dioxo-28,33-dioxa-20,34λ<sup>6</sup>-dithia-1,14,15,16-tetraazaheptacyclo[27.5.3.1<sup>3,7</sup>.1<sup>9,13</sup>.0<sup>12,16</sup>.0<sup>21,26</sup>.0<sup>32,36</sup>]nonatriaconta-3(39),4,6,9(38),10,12,14,21,23,25,29,31,36-tridecaen-8-yl]acetic acid

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**STEP A1 : Preparation of ethyl (2E)-3-(4-methyl-1-{3-[(oxan-2-yl)oxy]propyl}-1H-benzotriazol-5-yl)prop-2-enoate**

5

To a solution of ethyl (2E)-3-[1-(3-hydroxypropyl)-4-methyl-1H-benzotriazol-5-yl]prop-2-enoate (1 eq., 4.34 g, 15 mmol) in DCM (50 mL) at 0 °C 4-methylbenzene-1-sulfonic acid monohydrate (0.01 eq., 38 mg, 0.15 mmol) was added followed by addition of 3,4-dihydro-2H-pyran (1.1 equiv., 1.39 g, 16.5 mmol). The reaction mixture was allowed to warm to RT and was stirred for 1 h before quenching with saturated NaHCO<sub>3</sub> (30 mL). The phases were separated. The aq. phase was extracted with DCM (30 mL), and the combined organic phases were dried over MgSO<sub>4</sub>. The solvent was removed under reduced pressure to give the title compound (5.5 g, 98% yield).

<sup>1</sup>H-NMR (500 MHz, DMSO-d<sub>6</sub>) δ ppm: 8.02 (d, 1 H), 7.97 (d, 1 H), 7.71 (d, 1 H), 6.65 (d, 1 H), 4.77 (t, 2 H), 4.47 (dd, 1 H), 4.22 (q, 2 H), 3.65/3.36 (m+m, 2 H), 3.62/3.29 (m+m, 2 H), 2.81 (s, 3 H), 2.16 (m, 2 H), 1.71-1.32 (m, 6 H), 1.28 (t, 3 H)

**STEP 1 : Preparation of ethyl 3-[3-(hydroxymethyl)-4-methylphenyl]-3-(4-methyl-1-{3-[(oxan-2-yl)oxy]propyl}-1H-benzotriazol-5-yl)propanoate**

20

Ethyl (2E)-3-(4-methyl-1-{3-[(oxan-2-yl)oxy]propyl}-1H-benzotriazol-5-yl)prop-2-enoate (1 eq., 5.5 g, 0.015 mol) was added to dioxane (90 mL) and water (45 mL) and the suspension was degassed with nitrogen. [2-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]methanol (1.5 equiv., 5.5 g, 0.022 mol) and TEA (1.6 eq., 2.4 g, 0.024 mol) were

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added prior to the addition of chloro(1,5-cyclooctadiene)rhodium(I) dimer catalyst (0.05 equiv., 0.36 g, 0.00074 mol). The reaction mixture was heated at 80°C for 30 minutes, then stirred at RT overnight. After the reaction was completed, the mixture was diluted with water (50 mL). The solution was extracted with EtOAc (2x50 mL). The combined organic layer was washed with brine (50 mL), and dried over MgSO<sub>4</sub>. The solvent was evaporated to give a dark oil, which was purified by flash chromatography using heptane / EtOAc (50:50) as an eluent to give the title compound (7.3 g, quant.)

**<sup>1</sup>H-NMR** (500 MHz, DMSO-d<sub>6</sub>) δ ppm: 7.6 (d, 1 H), 7.47 (d, 1 H), 7.26 (d, 1 H), 7.1 (dd, 1 H), 7.02 (d, 1 H), 4.99 (t, 1 H), 4.83 (t, 1 H), 4.71 (t, 2 H), 4.45 (dd, 1 H), 4.4 (d, 2 H), 3.92 (q, 2 H), 3.62/3.33 (m+m, 2 H), 3.59/3.26 (m+m, 2 H), 3.13 (m, 2 H), 2.76 (s, 3 H), 2.15 (s, 3 H), 2.13 (m, 2 H), 1.7-1.3 (m, 6 H), 1.01 (t, 3 H)

**STEP 2 : Preparation of ethyl 3-(3-{[6-(benzyloxy)-2,2-dioxo-2*H*-1,2λ<sup>6</sup>,3-benzoxathiazin-3(4*H*)-yl]methyl}-4-methylphenyl)-3-(4-methyl-1-{3-[(oxan-2-yl)oxy]propyl}-1*H*-benzotriazol-5-yl)propanoate**

Ethyl 3-[3-(hydroxymethyl)-4-methylphenyl]-3-(4-methyl-1-{3-[(oxan-2-yl)oxy]propyl}-1*H*-benzotriazol-5-yl)propanoate (1 eq., 3.0 g, 6.1 mmol) was dissolved in THF (20 mL), then 6-(benzyloxy)-3,4-dihydro-2*H*-1,2λ<sup>6</sup>,3-benzoxathiazine-2,2-dione (1 eq., 1.80 g, 6.18 mmol) and PPh<sub>3</sub> (2 eq., 3.20 g, 12.2 mmol) were added. The mixture was cooled to 5 °C, DIAD (2 eq., 2.40 g, 11.9 mmol) was added dropwise and the reaction mixture was stirred at RT for 2h. The solvent was evaporated to dryness. The crude product was purified by normal phase silica gel chromatography using heptane-EtOAc (100:0 to 50:50) as an eluent to give the title compound (2.8 g, 60% yield).

**<sup>1</sup>H-NMR** (500 MHz, DMSO-d<sub>6</sub>) δ ppm: 7.58 (d, 1 H), 7.49-7.31 (m, 5 H), 7.49 (d, 1 H), 7.22 (d, 1 H), 7.19 (dd, 1 H), 7.13 (d, 1 H), 7.13 (d, 1 H), 7.07 (dd, 1 H), 6.96 (d, 1 H), 5.1 (s, 2 H), 4.85 (t, 1 H), 4.68 (t, 2 H), 4.43 (s, 2 H), 4.42 (dd, 1 H), 4.21 (s, 2 H), 3.92 (q, 2 H), 3.6/3.31 (m+m, 2 H), 3.57/3.24 (m+m, 2 H), 3.2/3.15 (dd+dd, 2 H), 2.77 (s, 3 H), 2.22 (s, 3 H), 2.11 (m, 2 H), 1.69-1.26 (m, 6 H), 0.99 (t, 3 H)

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**STEP 3 : Preparation of ethyl 3-{3-[(6-hydroxy-2,2-dioxo-2*H*-1,2λ<sup>6</sup>,3-benzoxathiazin-3(4*H*)-yl)methyl]-4-methylphenyl}-3-(4-methyl-1-{3-[(oxan-2-yl)oxy]propyl}-1*H*-benzotriazol-5-yl)propanoate**

5 Ethyl 3-(3-{[6-(benzyloxy)-2,2-dioxo-2*H*-1,2λ<sup>6</sup>,3-benzoxathiazin-3(4*H*)-yl]methyl}-4-methylphenyl)-3-(4-methyl-1-{3-[(oxan-2-yl)oxy]propyl}-1*H*-benzotriazol-5-yl)propanoate (1 eq., 2.80 g, 3.6 mmol) was dissolved in THF (45 mL) in an oven-dried vessel equipped with a PTFE-coated magnetic stir bar. Pd/C was added and the mixture was hydrogenated under 4 bar pressure at RT for 12 h. After completion of the reaction the catalyst was filtered off. The mother  
 10 liquid was evaporated to dryness to give the title compound (2.45 g, 99% yield).  
<sup>1</sup>H-NMR (500 MHz, DMSO-d<sub>6</sub>) δ ppm: 9.7 (s, 1 H), 7.6 (d, 1 H), 7.51 (d, 1 H), 7.21 (d, 1 H), 7.19 (dd, 1 H), 7.13 (d, 1 H), 6.99 (d, 1 H), 6.79 (dd, 1 H), 6.6 (d, 1 H), 4.84 (t, 1 H), 4.71 (t, 2 H), 4.43 (m, 1 H), 4.38 (s, 2 H), 4.21/4.17 (d+d, 2 H), 3.93 (q, 2 H), 3.61/3.33 (m+m, 2 H), 3.59/3.27 (m+m, 2 H), 3.19/3.15 (dd+dd, 2 H), 2.75 (s, 3 H), 2.22 (s, 3 H), 2.14 (qn, 2 H), 1.66-  
 15 1.31 (m, 6 H), 1 (t, 3 H)

**STEP 4 : Preparation of ethyl 3-{3-[(6-hydroxy-2,2-dioxo-2*H*-1,2λ<sup>6</sup>,3-benzoxathiazin-3(4*H*)-yl)methyl]-4-methylphenyl}-3-[1-(3-hydroxypropyl)-4-methyl-1*H*-benzotriazol-5-yl]propanoate**

20 Ethyl 3-{3-[(6-hydroxy-2,2-dioxo-2*H*-1,2λ<sup>6</sup>,3-benzoxathiazin-3(4*H*)-yl)methyl]-4-methylphenyl}-3-(4-methyl-1-{3-[(oxan-2-yl)oxy]propyl}-1*H*-benzotriazol-5-yl)propanoate (1 eq., 2.40 g, 3.60 mmol) was dissolved in EtOH (25.0 mL) and the 4-methylbenzene-1-sulfonic acid pyridine complex (0.05 eq., 45.3 mg, 0.180 mmol) was added. The reaction mixture was  
 25 stirred at 55 °C for 2h. The reaction mixture was concentrated, the residue was dissolved in DCM, washed with 2x20 ml of NaHCO<sub>3</sub>, then with 20 ml brine, dried over MgSO<sub>4</sub>, filtered and evaporated to dryness to give the title compound (1.90 g, 88% yield).  
<sup>1</sup>H-NMR (500 MHz, DMSO-d<sub>6</sub>) δ ppm: 9.71 (brs., 1 H), 7.6 (d, 1 H), 7.5 (d, 1 H), 7.22 (d, 1 H), 7.19 (dd, 1 H), 7.13 (d, 1 H), 6.99 (d, 1 H), 6.79 (dd, 1 H), 6.6 (d, 1 H), 4.84 (t, 1 H), 4.68

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(t, 2 H), 4.67 (br., 1 H), 4.4/4.36 (d+d, 2 H), 4.21/4.17 (d+d, 2 H), 3.94 (q, 2 H), 3.38 (t, 2 H), 3.19/3.15 (dd+dd, 2 H), 2.76 (s, 3 H), 2.22 (s, 3 H), 2.01 (m, 2 H), 1 (t, 3 H)

**STEP 5 : Preparation of ethyl 3-[1-(3-chloropropyl)-4-methyl-1*H*-benzotriazol-5-yl]-3-{3-[(6-hydroxy-2,2-dioxo-2*H*-1,2λ<sup>6</sup>,3-benzoxathiazin-3(4*H*)-yl)methyl]-4-methylphenyl}propanoate**

Using General Procedure 10 starting from ethyl 3-{3-[(6-hydroxy-2,2-dioxo-2*H*-1,2λ<sup>6</sup>,3-benzoxathiazin-3(4*H*)-yl)methyl]-4-methylphenyl}-3-[1-(3-hydroxypropyl)-4-methyl-1*H*-benzotriazol-5-yl]propanoate (1 eq.) as a reactant, the title compound (97% yield) was obtained.

**<sup>1</sup>H-NMR** (500 MHz, DMSO-d<sub>6</sub>) δ ppm: 9.76 (brs, 1 H), 7.63 (d, 1 H), 7.53 (d, 1 H), 7.22 (d, 1 H), 7.2 (dd, 1 H), 7.13 (d, 1 H), 6.99 (d, 1 H), 6.8 (dd, 1 H), 6.6 (d, 1 H), 4.84 (t, 1 H), 4.77 (t, 2 H), 4.37 (s, 2 H), 4.21/4.17 (d+d, 2 H), 3.93 (q, 2 H), 3.61 (t, 2 H), 3.19/3.15 (dd+dd, 2 H), 2.76 (s, 3 H), 2.33 (qn, 2 H), 2.22 (s, 3 H), 1 (t, 3 H)

**STEP 6 : Preparation of ethyl 3-{3-[(6-hydroxy-2,2-dioxo-2*H*-1,2λ<sup>6</sup>,3-benzoxathiazin-3(4*H*)-yl)methyl]-4-methylphenyl}-3-[1-(3-{[2-(hydroxymethyl)phenyl]sulfanyl}propyl)-4-methyl-1*H*-benzotriazol-5-yl]propanoate**

Ethyl 3-[1-(3-chloropropyl)-4-methyl-1*H*-benzotriazol-5-yl]-3-{3-[(6-hydroxy-2,2-dioxo-2*H*-1,2λ<sup>6</sup>,3-benzoxathiazin-3(4*H*)-yl)methyl]-4-methylphenyl}propanoate (1 eq., 1.61 g, 2.63 mmol) and (2-sulfanylphenyl)methanol (1.2 eq., 442 mg, 3.15 mmol) were dissolved in DMF (9 mL) and K<sub>2</sub>CO<sub>3</sub> (2 eq., 726 mg, 5.25 mmol) was added. The reaction mixture was stirred at RT for 2h. After pouring into 10 ml of water, the mixture was extracted with 2x30 mL of DCM. The combined organic layer was dried over MgSO<sub>4</sub>, filtered and evaporated to dryness to give a yellow crystalline product (1.5 g, 79% yield).

**<sup>1</sup>H-NMR** (500 MHz, DMSO-d<sub>6</sub>) δ ppm: 9.7 (s, 1 H), 7.59 (d, 1 H), 7.51 (d, 1 H), 7.43 (d, 1 H), 7.22 (d, 1 H), 7.19 (dd, 1 H), 7.19 (d, 1 H), 7.17 (t, 1 H), 7.13 (d, 1 H), 7.12 (t, 1 H), 6.99 (d, 1

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H), 6.79 (dd, 1 H), 6.6 (d, 1 H), 5.22 (t, 1 H), 4.84 (t, 1 H), 4.76 (t, 2 H), 4.52 (d, 2 H), 4.4/4.35 (d+d, 2 H), 4.21/4.17 (d+d, 2 H), 3.93 (q, 2 H), 3.19/3.13 (dd+dd, 2 H), 2.9 (t, 2 H), 2.76 (s, 3 H), 2.22 (s, 3 H), 2.13 (qn, 2 H), 1 (t, 3 H)

5     **STEP 7 : Preparation of ethyl 3-[1-(3-{[2-(chloromethyl)phenyl]sulfanyl}propyl)-4-methyl-1*H*-benzotriazol-5-yl]-3-{3-[(6-hydroxy-2,2-dioxo-2*H*-1,2λ<sup>6</sup>,3-benzoxathiazin-3(4*H*)-yl)methyl]-4-methylphenyl}propanoate**

Using General Procedure 10 starting from ethyl 3-{3-[(6-hydroxy-2,2-dioxo-2*H*-1,2λ<sup>6</sup>,3-benzoxathiazin-3(4*H*)-yl)methyl]-4-methylphenyl}-3-[1-(3-{[2-(hydroxymethyl)phenyl]sulfanyl}propyl)-4-methyl-1*H*-benzotriazol-5-yl]propanoate (1 eq.) as a reactant, the title compound (98% yield) was obtained.

**HRMS** calculated for C<sub>37</sub>H<sub>39</sub>ClN<sub>4</sub>O<sub>6</sub>S<sub>2</sub>: 734.2000; [M+H]<sup>+</sup> found: 735.2057 (δ = -2.1 ppm)

15     **STEP 8 : Preparation of ethyl [4,38-dimethyl-34,34-dioxo-28,33-dioxo-20,34λ<sup>6</sup>-dithia-1,14,15,16-tetraazaheptacyclo[27.5.3.1<sup>3,7</sup>.1<sup>9,13</sup>.0<sup>12,16</sup>.0<sup>21,26</sup>.0<sup>32,36</sup>]nonatriaconta-3(39),4,6,9(38),10,12,14,21,23,25,29,31,36-tridecaen-8-yl]acetate**

Using General Procedure 11 starting from ethyl 3-[1-(3-{[2-(chloromethyl)phenyl]sulfanyl}propyl)-4-methyl-1*H*-benzotriazol-5-yl]-3-{3-[(6-hydroxy-2,2-dioxo-2*H*-1,2λ<sup>6</sup>,3-benzoxathiazin-3(4*H*)-yl)methyl]-4-methylphenyl}propanoate (1 eq., 1.56 g, 2.12 mmol) as a reactant, the title compound (1.375 g, yellow crystals, 93% yield) was obtained.

**HRMS** calculated for C<sub>37</sub>H<sub>38</sub>N<sub>4</sub>O<sub>6</sub>S<sub>2</sub>: 698.2233; [M+H]<sup>+</sup> found: 699.229 (δ = -2.2 ppm)

25     **STEP 9 : Preparation of EXAMPLE 67**

Using General Procedure 12 starting from ethyl [4,38-dimethyl-34,34-dioxo-28,33-dioxo-20,34λ<sup>6</sup>-dithia-1,14,15,16-tetraazaheptacyclo[27.5.3.1<sup>3,7</sup>.1<sup>9,13</sup>.0<sup>12,16</sup>.0<sup>21,26</sup>.0<sup>32,36</sup>]nonatriaconta-3(39),4,6,9(38),10,12,14,21,23,25,29,31,36-tridecaen-8-yl]acetate (1 eq.) as a reactant, the title compound (white solid, 22% yield) was obtained.



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The enantiopure products were obtained by chromatographic separation on chiral column.

**Example 67a (E1)**

**HRMS** calculated for  $C_{35}H_{34}N_4O_6S_2$ : 670.1920;  $[M+H]^+$  found: 671.1992 ( $\delta = -0.1$  ppm)

5

**Example 67b (E2)**

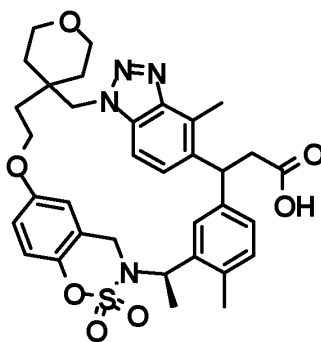
**HRMS** calculated for  $C_{35}H_{34}N_4O_6S_2$ : 670.1920;  $[M+H]^+$  found: 671.1992 ( $\delta = -0.1$  ppm)

**$^1H$ -NMR** (500 MHz, DMSO- $d_6$ )  $\delta$  ppm: 12.12 (br., 1 H), 7.61 (dd, 1 H), 7.57 (dd, 1 H), 7.54 (d, 1 H), 7.46 (d, 1 H), 7.41 (td, 1 H), 7.36 (dd, 1 H), 7.33 (td, 1 H), 7.18 (d, 1 H), 7.15 (m, 1 H), 7.15 (m, 1 H), 7.15 (d, 1 H), 6.77 (brs., 1 H), 5.26/5.14 (d+d, 2 H), 4.81 (t, 1 H), 4.64 (m, 2 H), 4.34/4.17 (d+d, 2 H), 4.25/4.11 (d+d, 2 H), 3.04 (m, 2 H), 3.01 (m, 2 H), 2.75 (s, 3 H), 2.29 (s, 3 H), 2.24/2.14 (m+m, 2 H)

**$^{13}C$ -NMR** (125 MHz, DMSO- $d_6$ )  $\delta$  ppm: 173.2, 131.3, 131.2, 130.2, 130, 129.7, 129.2, 127.3, 127.1, 119.6, 116.4, 113.4, 107.8, 68.9, 51.8, 49.2, 45.8, 41.3, 40.8, 30.6, 28.6, 18.4, 13.3

15

**EXAMPLE 68** : [(2*R*)-2,4,31-Trimethyl-27,27-dioxo-27 $\lambda^6$ -spiro[21,26-dioxa-27-thia-1,14,15,16-tetraazahexacyclo[20.5.3.1<sup>3,7</sup>.1<sup>9,13</sup>.0<sup>12,16</sup>.0<sup>25,29</sup>]dotriacont-3(32),4,6,9(31),10,12,14,22,24,29-decaene-18,4'-oxan]-8-yl]acetic acid

20 **STEP A1 : Preparation of 4-[2-(benzyloxy)ethyl]oxane-4-carbonitrile**

To a solution of oxane-4-carbonitrile (1 eq., 10 g, 90 mmol) in abs. THF (20 mL/g, 200 mL) lithium bis(trimethylsilyl)amide (1.2 eq., 1 M in THF, 108 mL, 108 mmol) was added dropwise

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at -78°C while continuous stirring and the mixture was stirred at this temperature for additional 2 h. [(2-Iodoethoxy)methyl]benzene (1 eq., 23.58 g, 90 mmol) dissolved in 100 mL of THF was added dropwise at -78°C. The reaction mixture was allowed to warm to RT and the stirring at RT was continued over a week-end. After completion of the reaction the mixture was quenched with 100 mL water. 500 mL of EtOAc was added and the layers were separated. The organic layer was washed with further 300 mL of brine, dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated to dryness to give the crude product, which ~~It~~ was purified by normal phase silica gel chromatography using heptane-EtOAc (0 to 60:40) as an eluent to give the title compound (12.3 g, 56% yield).

10 <sup>1</sup>H-NMR (400 MHz, DMSO-d<sub>6</sub>) δ ppm: 7.3 (m, 5 H), 4.49 (s, 2 H), 3.84/3.49 (m, 4 H), 3.62 (t, 2 H), 1.9 (t, 2 H), 1.83/1.6 (2m, 4 H)

#### STEP A2 : Preparation of 1-{4-[2-(benzyloxy)ethyl]oxan-4-yl}methanamine

15 Lithium aluminium hydride (1.5 eq., 2.85 g, 75 mmol) was placed into a round bottom flask. After addition of abs. THF (10 mL/g, 123 ml) the mixture was cooled to 10 °C. A solution of 4-[2-(benzyloxy)ethyl]oxane-4-carbonitrile (1 eq., 12.3 g, 50 mmol) in abs. THF (10 mL/g, 123 mL) was added dropwise over a period of 20 min at 10°C while continuous stirring. The reaction mixture was allowed to warm to RT and was stirred for further 5 h. After completion of the reaction the mixture was cooled to 0°C, quenched with aq. NaOH, then with aq. Na<sub>2</sub>SO<sub>4</sub> solution. After stirring overnight at RT, the mixture was filtered, washed with EtOAc and the mother liquor was concentrated to dryness to give the title compound (12.1 g, 90% yield).

20 <sup>1</sup>H-NMR (400 MHz, DMSO-d<sub>6</sub>) δ ppm: 7.37-7.23 (m, 4 H), 4.44 (s, 2 H), 3.57-3.49 (m, 4 H), 3.48 (t, 2 H), 2.48 (s, 2 H), 1.66 (t, 2 H), 1.41-1.26 (m, 4 H)

25

#### STEP A3 : Preparation of *N*-({4-[2-(benzyloxy)ethyl]oxan-4-yl}methyl)-3-methyl-2-nitroaniline

Using General Procedure 2 STEP 1 starting from 1-{4-[2-(benzyloxy)ethyl]oxan-4-yl}methanamine (1 eq.) as a reactant, the title compound (orange oil, 52% yield) was obtained.

30

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<sup>1</sup>H-NMR (400 MHz, DMSO-d<sub>6</sub>) δ ppm: 7.38-7.24 (m, 5 H), 7.27 (m, 1 H), 6.82 (d, 1 H), 6.59 (d, 1 H), 6.46 (t, 1 H), 4.42 (s, 2 H), 3.57 (t, 2 H), 3.52-3.47 (m, 4 H), 3.33 (dt, 2 H), 2.31 (s, 3 H), 1.79 (quint, 2 H)

5     **STEP A4 : Preparation of *N*-({4-[2-(benzyloxy)ethyl]oxan-4-yl}methyl)-4-bromo-3-methyl-2-nitroaniline**

Using General Procedure 2 STEP 2 starting from *N*-({4-[2-(benzyloxy)ethyl]oxan-4-yl}methyl)-3-methyl-2-nitroaniline (1 eq.) as a reactant, the title compound (78% yield) was  
10     obtained.

<sup>1</sup>H-NMR (400 MHz, DMSO-d<sub>6</sub>) δ ppm: 7.49 (d, 1 H), 7.35-7.22 (m, 5 H), 6.91 (d, 1 H), 5.99 (t, 1 H), 4.43 (s, 2 H), 3.62-3.5 (m, 4 H), 3.51 (t, 2 H), 3.19 (g, 2 H), 2.28 (s, 3 H), 2.28 (t, 2 H), 1.45/1.33 (m, 4 H)

15     **STEP A5 : Preparation of *N*<sup>1</sup>-({4-[2-(benzyloxy)ethyl]oxan-4-yl}methyl)-4-bromo-3-methylbenzene-1,2-diamine**

Using General Procedure 2 STEP 3 starting from *N*-({4-[2-(benzyloxy)ethyl]oxan-4-yl}methyl)-4-bromo-3-methyl-2-nitroaniline (1 eq.) as a reactant, the title compound (97%  
20     yield) was obtained.

<sup>1</sup>H-NMR (400 MHz, DMSO-d<sub>6</sub>) δ ppm: 7.29 (m, 5 H), 6.7 (d, 1 H), 6.35 (d, 1 H), 4.7 (m, 2 H), 4.4 (s, 2 H), 4.1 (m, 1 H), 3.6 (m, 4 H), 3.5 (t, 2 H), 2.99 (s, 2 H), 2.2 (s, 3 H), 1.87 (t, 2 H), 1.6-1.4 (m, 4 H)

25     **STEP A6 : Preparation of 1-({4-[2-(benzyloxy)ethyl]oxan-4-yl}methyl)-5-bromo-4-methyl-1*H*-benzotriazole**

Using General Procedure 2 STEP 4 starting from *N*<sup>1</sup>-({4-[2-(benzyloxy)ethyl]oxan-4-yl}methyl)-4-bromo-3-methylbenzene-1,2-diamine (1 eq.) as a reactant, the title compound  
30     (brown solid, 80% yield) was obtained.

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<sup>1</sup>H-NMR (400 MHz, DMSO-d<sub>6</sub>) δ ppm: 7.69 (m, 2 H), 7.4-7.3 (m, 5 H), 4.7 (s, 2 H), 4.48 (s, 2 H), 3.68/3.52 (m, 4 H), 3.61 (t, 2 H), 2.71 (s, 3 H), 1.71 (t, 2 H), 1.45 (m, 4 H)

**STEP A7 : Preparation of ethyl (2E)-3-[1-({4-[2-(benzyloxy)ethyl]oxan-4-yl}methyl)-4-methyl-1H-benzotriazol-5-yl]prop-2-enoate**

The mixture of 1-({4-[2-(benzyloxy)ethyl]oxan-4-yl}methyl)-5-bromo-4-methyl-1H-benzotriazole (1 eq., 3 g, 6.75 mmol), ethyl (2E)-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)prop-2-enoate (1.1 eq., 1.68 g, 7.43 mmol), sodium carbonate (2.5 eq., 1.79 g, 16.9 mmol), A<sup>la</sup>phos.PdCl<sub>2</sub> catalyst (0.05 eq., 149 mg, 0.3375 mmol), THF (5 mL/mmol, 34 mL) and water (5 mL/mmol, 34 mL) was heated at reflux temperature for 2 h under nitrogen atmosphere. After the completion of the reaction the solvent was evaporated under reduced pressure. The residue was purified by normal phase silica gel chromatography using heptane-EtOAc (0 to 50:50) as an eluent to give the title compound (2.61 g, 79% yield).

<sup>1</sup>H-NMR (400 MHz, DMSO-d<sub>6</sub>) δ ppm: 8.01 (d, 1 H), 7.96 (d, 1 H), 7.7 (d, 1 H), 7.3 (m, 5 H), 6.64 (d, 1 H), 4.7 (s, 2 H), 4.48 (s, 2 H), 4.21 (q, 2 H), 3.65/3.53 (m, 4 H), 3.63 (t, 2 H), 2.8 (s, 3 H), 1.72 (t, 2 H), 1.45 (m, 4 H), 1.29 (t, 3 H)

**STEP 1 : Preparation of ethyl 3-[1-({4-[2-(benzyloxy)ethyl]oxan-4-yl}methyl)-4-methyl-1H-benzotriazol-5-yl]-3-{3-[(1S)-1-hydroxyethyl]-4-methylphenyl}propanoate**

Using General Procedure 6 starting from ethyl (2E)-3-[1-({4-[2-(benzyloxy)ethyl]oxan-4-yl}methyl)-4-methyl-1H-benzotriazol-5-yl]prop-2-enoate (1 eq.) and (1S)-1-[2-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]ethan-1-ol (2 eq.) as reactants, the title compound (30% yield) was obtained.

<sup>1</sup>H-NMR (400 MHz, DMSO-d<sub>6</sub>) δ ppm: 7.6 (d, 1 H), 7.45 (d, 1 H), 7.4 (d, 1 H), 7.3 (m, 5 H), 7.05 (dd, 1 H), 7 (d, 1 H), 5 (d, 1 H), 4.8 (m, 2 H), 4.65 (s, 2 H), 4.5 (s, 2 H), 3.9 (q, 2 H), 3.65/3.5 (m, 4 H), 3.1 (m, 2 H), 2.8 (d, 3 H), 2.65 (m, 2 H), 2.2 (s, 3 H), 1.7 (t, 2 H), 1.4 (m, 4 H), 1.25 (d, 3 H), 1 (t, 3 H)

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**STEP 2 : Preparation of ethyl 3-(3-((1*R*)-1-[6-(benzyloxy)-2,2-dioxo-2*H*-1,2λ<sup>6</sup>,3-benzoxathiazin-3(4*H*)-yl]ethyl)-4-methylphenyl)-3-[1-({4-[2-(benzyloxy)ethyl]oxan-4-yl}methyl)-4-methyl-1*H*-benzotriazol-5-yl]propanoate**

5

Using General Procedure 7 starting from ethyl 3-[1-({4-[2-(benzyloxy)ethyl]oxan-4-yl}methyl)-4-methyl-1*H*-benzotriazol-5-yl]-3-{3-[(1*S*)-1-hydroxyethyl]-4-methylphenyl}propanoate (1 eq.) and 6-(benzyloxy)-3,4-dihydro-2*H*-1,2λ<sup>6</sup>,3-benzoxathiazine-2,2-dione (1.1 eq.) as reactants, the title compound (48% yield) was obtained.

10 **<sup>1</sup>H-NMR** (400 MHz, DMSO-d<sub>6</sub>) δ ppm: 7.59 (d, 1 H), 7.52 (d, 1 H), 7.46/7.24 (m, 11 H), 7.13 (m, 2 H), 7.04 (m, 1 H), 7 (m, 1 H), 6.89/6.82 (d, 1 H), 5.26 (q, 1 H), 5.07 (m, 2 H), 4.87 (m, 1 H), 4.6 (sl, 2 H), 4.44 (sl, 2 H), 4.41/4.32 (d, 2 H), 3.92 (q, 2 H), 3.64/3.52 (m, 4 H), 3.61 (m, 2 H), 3.2 (m, 2 H), 2.77 (s, 3 H), 2.28 (s, 3 H), 1.68 (m, 2 H), 1.44-1.37 (m, 3 H), 1.4 (d, 4 H), 0.96 (t, 3 H)

15

**STEP 3 : Preparation of ethyl 3-{3-[(1*R*)-1-(6-hydroxy-2,2-dioxo-2*H*-1,2λ<sup>6</sup>,3-benzoxathiazin-3(4*H*)-yl)ethyl]-4-methylphenyl}-3-[1-({4-[2-(benzyloxy)ethyl]oxan-4-yl}methyl)-4-methyl-1*H*-benzotriazol-5-yl]propanoate**

20 Using General Procedure 8 starting from ethyl 3-(3-((1*R*)-1-[6-(benzyloxy)-2,2-dioxo-2*H*-1,2λ<sup>6</sup>,3-benzoxathiazin-3(4*H*)-yl]ethyl)-4-methylphenyl)-3-[1-({4-[2-(benzyloxy)ethyl]oxan-4-yl}methyl)-4-methyl-1*H*-benzotriazol-5-yl]propanoate (1 eq.) as a reactant, the title compound (96% yield) was obtained.

25 **<sup>1</sup>H-NMR** (400 MHz, DMSO-d<sub>6</sub>) δ ppm: 10.6 (s, 1 H), 7.65 (d, 1 H), 7.6 (d, 1 H), 7.5 (d, 1 H), 7.15 (m, 2 H), 6.9 (d, 1 H), 6.7 (m, 1 H), 6.6 (d, 1 H), 5.3 (m, 1 H), 4.9 (m, 1 H), 4.6 (s, 2 H), 4.5 (t, 1 H), 4.4/4.3 (s+d, 2 H), 3.95 (q, 2 H), 3.65/3.5 (m, 6 H), 3.2 (d, 2 H), 2.8 (s, 3 H), 2.3 (s, 3 H), 1.6 (t, 2 H), 1.4 (m, 7 H), 1 (t, 3 H)

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**STEP 4 : Preparation of ethyl 3-(1-{[4-(2-chloroethyl)oxan-4-yl]methyl}-4-methyl-1*H*-benzotriazol-5-yl)-3-{3-[(1*R*)-1-(6-hydroxy-2,2-dioxo-2*H*-1,2λ<sup>6</sup>,3-benzoxathiazin-3(4*H*)-yl)ethyl]-4-methylphenyl}-3-(1-{[4-(2-hydroxyethyl)oxan-4-yl]methyl}-4-methyl-1*H*-benzotriazol-5-yl)propanoate**

5 Using General Procedure 10 starting from ethyl 3-{3-[(1*R*)-1-(6-hydroxy-2,2-dioxo-2*H*-1,2λ<sup>6</sup>,3-benzoxathiazin-3(4*H*)-yl)ethyl]-4-methylphenyl}-3-(1-{[4-(2-hydroxyethyl)oxan-4-yl]methyl}-4-methyl-1*H*-benzotriazol-5-yl)propanoate (1 eq.) as a reactant, the title compound (17% yield) was obtained.

<sup>1</sup>**H-NMR** (400 MHz, DMSO-d<sub>6</sub>) δ ppm: 9.65 (s, 1 H), 7.68 (d, 1 H), 7.6 (d, 1 H), 7.45 (d, 1 H),  
 10 7.15 (m, 2 H), 6.91 (d, 1 H), 6.71 (m, 1 H), 6.6 (d, 1 H), 5.25 (m, 1 H), 4.89 (m, 1 H), 4.68 (s, 2 H), 4.4/4.3 (s+d, 2 H), 3.91 (q, 2 H), 3.81 (t, 2 H), 3.69/3.55 (m, 4 H), 3.21 (d, 2 H), 2.79 (s, 3 H), 2.29 (s, 3 H), 1.85 (t, 2 H), 1.5-1.3 (m+d, 7 H), 1 (2t, 3 H)

**STEP 5 : Preparation of ethyl [(2*R*)-2,4,31-trimethyl-27,27-dioxo-27λ<sup>6</sup>-spiro[21,26-dioxa-27-thia-1,14,15,16-tetraazahexacyclo[20.5.3.1<sup>3,7</sup>.1<sup>9,13</sup>.0<sup>12,16</sup>.0<sup>25,29</sup>]dotriaconta-3(32),4,6,9(31),10,12,14,22,24,29-decaene-18,4'-oxan]-8-yl]acetate**

Using General Procedure 11 starting from ethyl 3-(1-{[4-(2-chloroethyl)oxan-4-yl]methyl}-4-methyl-1*H*-benzotriazol-5-yl)-3-{3-[(1*R*)-1-(6-hydroxy-2,2-dioxo-2*H*-1,2λ<sup>6</sup>,3-benzoxathiazin-3(4*H*)-yl)ethyl]-4-methylphenyl}propanoate (1 eq.) as a reactant, the title compound (91% yield) was obtained.

<sup>1</sup>**H-NMR** (400 MHz, DMSO-d<sub>6</sub>) δ ppm: 0.91 - 1.12 (m, 23 H) 1.15 - 1.33 (m, 11 H) 1.37 - 1.51 (m, 13 H) 1.58 - 1.74 (m, 25 H) 1.73 - 2.08 (m, 8 H) 2.19 - 2.39 (m, 22 H) 2.63 - 2.85 (m, 24 H)  
 25 2.92 - 3.24 (m, 11 H) 3.36 - 3.49 (m, 15 H) 3.57 - 3.81 (m, 22 H) 3.83 - 4.02 (m, 19 H) 4.26 - 4.40 (m, 8 H) 4.55 - 4.66 (m, 11 H) 4.70 - 4.92 (m, 13 H) 5.06 (dd, J=10.76, 5.99 Hz, 4 H) 5.26 (t, J=6.66 Hz, 7 H) 5.57 (br. s., 1 H) 5.68 (s, 1 H) 5.72 (d, J=6.85 Hz, 2 H) 6.49 - 6.79 (m, 8 H) 6.84 - 6.99 (m, 7 H) 7.05 - 7.23 (m, 12 H) 7.26 - 7.50 (m, 7 H) 7.52 - 7.66 (m, 8 H) 7.73 (d, J=8.68 Hz, 1 H) 7.80 (d, J=8.68 Hz, 1 H) 7.90 (d, J=8.68 Hz, 1 H)

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**STEP 6 : Preparation of EXAMPLE 68**

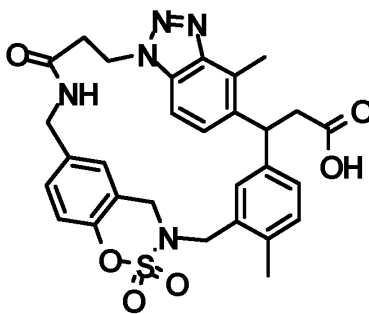
Using General Procedure 12 starting from ethyl [(2*R*)-2,4,31-trimethyl-27,27-dioxo-27 $\lambda^6$ -spiro[21,26-dioxa-27-thia-1,14,15,16-tetraazahexacyclo[20.5.3.1<sup>3,7</sup>.1<sup>9,13</sup>.0<sup>12,16</sup>.0<sup>25,29</sup>]

5 dotriaconta-3(32),4,6,9(31),10,12,14,22,24,29-decaene-18,4'-oxan]-8-yl]acetate (1 eq.) as a reactant, the title compound (59% yield) was obtained.

**HRMS** calculated for C<sub>34</sub>H<sub>38</sub>N<sub>4</sub>O<sub>7</sub>S: 646.2461; [M+H]<sup>+</sup> found: 647.2535 ( $\delta$ =0.2 ppm)

**<sup>1</sup>H-NMR** (400 MHz, DMSO-d<sub>6</sub>)  $\delta$  ppm: 1.16 (d, J=6.36 Hz, 2 H) 1.24 (d, J=6.72 Hz, 4 H) 1.52  
 - 1.77 (m, 7 H) 1.78 - 1.96 (m, 5 H) 1.98 - 2.11 (m, 2 H) 2.29 (s, 4 H) 2.31 - 2.36 (m, 3 H) 2.62  
 10 - 2.69 (m, 5 H) 2.81 (d, J=15.53 Hz, 4 H) 2.95 (dd, J=16.20, 6.66 Hz, 2 H) 3.14 - 3.23 (m, 3 H)  
 3.43 (d, J=17.85 Hz, 3 H) 3.59 - 3.82 (m, 8 H) 3.83 - 3.93 (m, 2 H) 4.06 - 4.17 (m, 2 H) 4.52 -  
 4.72 (m, 3 H) 4.73 - 4.82 (m, 3 H) 4.93 (br. s., 1 H) 5.26 (q, J=6.44 Hz, 3 H) 5.53 (d, J=2.69 Hz,  
 2 H) 6.60 - 6.76 (m, 3 H) 6.85 - 6.96 (m, 4 H) 7.14 (s, 2 H) 7.19 (d, J=7.82 Hz, 2 H) 7.31 (d,  
 J=7.95 Hz, 1 H) 7.39 - 7.50 (m, 2 H) 7.73 (d, J=8.80 Hz, 1 H) 7.78 (d, J=8.68 Hz, 1 H) 7.85 -  
 15 7.93 (m, 1 H) 12.28 (br. s., 1 H)

**EXAMPLE 69** : [4,31-Dimethyl-19,27,27-trioxo-26-oxa-27 $\lambda^6$ -thia-1,14,15,16,20-pentaazahexacyclo[20.5.3.1<sup>3,7</sup>.1<sup>9,13</sup>.0<sup>12,16</sup>.0<sup>25,29</sup>]dotriaconta-3(32),4,6,9(31),10,12,14,22,24,29-decaen-8-yl]acetic acid



20

**STEP A1 : Preparation of 3-{5-[(1*E*)-3-ethoxy-3-oxoprop-1-en-1-yl]-4-methyl-1*H*-benzotriazol-1-yl}propanoic acid**

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Ethyl (2*E*)-3-[1-(3-hydroxypropyl)-4-methyl-1*H*-benzotriazol-5-yl]prop-2-enoate (1 eq., 2 g, 6.91 mmol) was dissolved in MeCN (10 mL) and water (10 mL), then 3-iodo-1,2-phenylene diacetate (2.2 eq., 4.90 g, 15.2 mmol) and (2,2,6,6-tetramethylpiperidin-1-yl)oxidanyl (0.2 eq., 0.216 g, 1.38 mmol) were added and the mixture was stirred at RT for 1h. After the completion of the reaction the mixture was quenched with aq. Na<sub>2</sub>S<sub>2</sub>O<sub>3</sub> solution, and aq. Na<sub>2</sub>CO<sub>3</sub> solution (25-25mL), then washed with EtOAc. The layers were separated and the pH of the aq. phase was adjusted with citric acid to 3-4. The mixture was extracted with EtOAc, the layers were separated, the organic layer was dried over MgSO<sub>4</sub>, filtered and concentrated under reduced pressure. The solid residue was treated with water, the precipitate was filtered-off and dried to give the title compound (1.731 g, 83% yield).

<sup>1</sup>H-NMR (400 MHz, DMSO-d<sub>6</sub>) δ ppm: 12.6 (m, 1 H), 8 (d, 1 H), 7.95 (d, 1 H), 7.7 (d, 1 H), 6.65 (d, 1 H), 4.9 (t, 2 H), 4.2 (q, 2 H), 3 (t, 2 H), 2.8 (sl, 3 H), 1.3 (t, 3 H)

**STEP A2 : Preparation of ethyl (2*E*)-3-{1-[3-(benzyloxy)-3-oxopropyl]-4-methyl-1*H*-benzotriazol-5-yl}prop-2-enoate**

3-{5-[(1*E*)-3-Ethoxy-3-oxoprop-1-en-1-yl]-4-methyl-1*H*-benzotriazol-1-yl}propanoic acid (1 eq., 1.724 g, 5.684 mmol) was dissolved in DCM (70 mL) under argon atm., then DMF (0.2 eq., 0.09 mL, 1.1 mmol) was added to the solution. The mixture was cooled to 0 °C, then oxalyl chloride (9 eq., 6.49 g, 4.33 mL, 51.1 mmol) was added. The reaction mixture was stirred at 0 °C for 15 min, then at RT for further 1h. The reaction mixture was concentrated and the residue was suspended in DCM (15 mL). Phenylmethanol (1.2 eq., 0.74 g, 0.71 mL, 6.82 mmol) was dissolved in DCM (20 mL) under argon atm. The suspension of the acyl chloride in DCM was added dropwise and the reaction mixture was stirred at RT overnight. The mixture was washed with water, then with brine. The organic phase was separated and dried over MgSO<sub>4</sub>, filtered and concentrated under reduced pressure. The residue was purified by normal phase silica gel chromatography using heptane-EtOAc as eluents to give the title compound (1.607 g, 72% yield).

<sup>1</sup>H-NMR (400 MHz, DMSO-d<sub>6</sub>) δ ppm: 8.05 (d, 1 H), 7.95 (d, 1 H), 7.7 (d, 1 H), 7.25 (2m, 5 H), 6.65 (d, 1 H), 5 (s, 2 H), 4.9 (t, 2 H), 4.2 (q, 2 H), 3.2 (t, 2 H), 2.8 (s, 3 H), 1.3 (t, 3 H)



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**STEP 1 : Preparation of ethyl 3-{1-[3-(benzyloxy)-3-oxopropyl]-4-methyl-1H-benzotriazol-5-yl}-3-[3-(hydroxymethyl)-4-methylphenyl]propanoate**

5 Using General Procedure 6 starting from ethyl (2E)-3-{1-[3-(benzyloxy)-3-oxopropyl]-4-methyl-1H-benzotriazol-5-yl}prop-2-enoate (1 eq., 0.859 g, 2.18 mmol) and [2-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]methanol (1.1 eq., 0.596 g, 2.40 mmol) as a reactant, the title compound (0.729 g, 62% yield) was obtained.

<sup>1</sup>H-NMR (400 MHz, DMSO-d<sub>6</sub>) δ ppm: 7.6 (d, 1 H), 7.5 (d, 1 H), 7.3/7.2 (m, 5 H), 7.3 (d, 1 H), 7.1 (dd, 1 H), 7 (d, 1 H), 5.05 (s, 2 H), 5 (t, 1 H), 4.85 (t, 3 H), 4.4 (d, 2 H), 3.9 (q, 2 H), 3.1 (m, 4 H), 2.8 (s, 3 H), 2.2 (s, 3 H), 1 (t, 3 H)

**STEP C1 : Preparation of *tert*-butyl 6-cyano-2,2-dioxo-2H-1,2λ<sup>6</sup>,3-benzoxathiazine-3(4H)-carboxylate**

15

6-Bromo-3,4-dihydro-2H-1,2λ<sup>6</sup>,3-benzoxathiazine-2,2-dione (1 eq., 5.95 g, 22.5 mmol) was dissolved in DCM (225 mL), then TEA (1.1 eq., 2.51 g, 3.45 mL, 24.8 mmol), *N,N*-dimethylpyridin-4-amine (0.1 eq., 275 mg, 2.25 mmol) and di-*tert*-butyl dicarbonate (1.1 eq., 5.41 g, 24.8 mmol) were added. The reaction mixture was stirred at RT for 2h. The mixture was poured into 500 mL 0.1 M HCl solution. The organic phase was separated, washed with 500 mL 0.1 M HCl solution (2x), dried over MgSO<sub>4</sub>, filtered and concentrated to give *tert*-butyl 6-bromo-2,2-dioxo-2H-1,2λ<sup>6</sup>,3-benzoxathiazine-3(4H)-carboxylate (quant.). The crude product (1 eq., 5 g, 13.73 mmol) was dissolved in *N,N*-dimethylacetamide (80 mL), then zinc (0.5 eq., 449 mg, 6.86 mmol) and zinc cyanide (1 eq., 1.612 g, 13.73 mmol) were added. The mixture was degassed with argon, then bis(tri-*tert*-butylphosphine)palladium(0) catalyst (0.1 eq., 424 mg, 1.73 mmol) was added. The reaction mixture was stirred at 80 °C for 4h. The mixture was filtered, the filtered solid was washed with EtOAc, the filtrate was concentrated under high vacuum. The residue was dissolved in EtOAc, then washed with brine. The organic phase was dried over MgSO<sub>4</sub>, filtered and concentrated under reduced pressure to give the crude product,

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which was purified by normal phase silica gel chromatography using heptane-EtOAc as eluents to give the title compound (2.704 g, 63% yield).

<sup>1</sup>H-NMR (400 MHz, DMSO-d<sub>6</sub>) δ ppm: 8.15 (d, 1 H), 8 (dd, 1 H), 7.6 (d, 1 H), 5.2 (s, 2 H), 1.5 (s, 9 H)

5

**STEP C2 : Preparation of benzyl [(2,2-dioxo-3,4-dihydro-2H-1,2λ<sup>6</sup>,3-benzoxathiazin-6-yl)methyl]carbamate**

10 *Tert*-butyl 6-cyano-2,2-dioxo-2H-1,2λ<sup>6</sup>,3-benzoxathiazine-3(4H)-carboxylate (1 eq., 1 g, 3.22 mmol) was dissolved in 7M NH<sub>3</sub> solution in MeOH (10 mL), and Raney nickel catalyst (5 eq., 945 mg, 16.11 mmol) was added. The reaction mixture was hydrogenated under atmospheric pressure for 4h. After the completion of the reaction the mixture was filtered, the filtrate was concentrated to give the crude 6-(aminomethyl)-3,4-dihydro-2H-1,2λ<sup>6</sup>,3-benzoxathiazine-2,2-

15 dione (66% yield), which was dissolved in THF (2.5 mL). NaHCO<sub>3</sub> (1.1 eq.) was added followed by a dropwise addition of benzyl chloroformate (1.1 eq.) and the mixture was stirred at RT for 2h. The mixture was diluted with water and EtOAc, the separated organic phase was washed with brine, dried over MgSO<sub>4</sub>, filtered, concentrated to give a crude product, which was purified by normal phase silica gel chromatography using heptane-EtOAc as eluents to give the title

20 compound (46% yield).

<sup>1</sup>H-NMR (400 MHz, DMSO-d<sub>6</sub>) δ ppm: 8.5 (m, 1 H), 7.8 (t, 1 H), 7.35 (m, 5 H), 7.2 (dd, 1 H), 7.15 (d, 1 H), 7 (d, 1 H), 5.05 (s, 2 H), 4.5 (s, 2 H), 4.2 (d, 2 H)

**STEP 2 : Preparation of ethyl 3-(3-{[6-({[(benzyloxy)carbonyl]amino}methyl)-2,2-dioxo-2H-1,2λ<sup>6</sup>,3-benzoxathiazin-3(4H)-yl]methyl}-4-methylphenyl)-3-{1-[3-(benzyloxy)-3-oxopropyl]-4-methyl-1H-benzotriazol-5-yl}propanoate**

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Using General Procedure 7 starting from benzyl [(2,2-dioxo-3,4-dihydro-2H-1,2λ<sup>6</sup>,3-benzoxathiazin-6-yl)methyl]carbamate (1 eq., 571 mg, 1.64 mmol) and ethyl 3-{1-[3-(benzyloxy)-3-oxopropyl]-4-methyl-1H-benzotriazol-5-yl}-3-[3-(hydroxymethyl)-4-

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methylphenyl] propanoate (1.1 eq., 930 mg, 1.80 mmol) as reactants, the title compound (1.017 g, 73% yield) was obtained.

<sup>1</sup>H-NMR (400 MHz, DMSO-d<sub>6</sub>) δ ppm: 7.85 (t, 1 H), 7.6 (d, 1 H), 7.5 (d, 1 H), 7.4-7.1 (m, 16 H), 5.05/5 (2s, 4 H), 4.9 (t, 2 H), 4.85 (m, 1 H), 4.5 (2d, 2 H), 4.2 (m, 4 H), 3.9 (q, 2 H), 3.2 (d, 2 H), 3.1 (t, 1 H), 2.8 (s, 3 H), 2.2 (s, 3 H), 1 (t, 3 H)

**STEP 3 : Preparation of 3-{5-[1-(3-{[6-(aminomethyl)-2,2-dioxo-2*H*-1,2λ<sup>6</sup>,3-benzoxathiazin-3(4*H*)-yl]methyl}-4-methylphenyl)-3-ethoxy-3-oxopropyl]-4-methyl-1*H*-benzotriazol-1-yl}propanoic acid**

10

Using General Procedure 8 starting from ethyl 3-(3-{[6-(((benzyloxy)carbonyl)amino)methyl]-2,2-dioxo-2*H*-1,2λ<sup>6</sup>,3-benzoxathiazin-3(4*H*)-yl]methyl}-4-methylphenyl)-3-{1-[3-(benzyloxy)-3-oxopropyl]-4-methyl-1*H*-benzotriazol-5-yl}propanoate (1 eq., 1.01 g, 1.19 mmol) as a reactant, the title compound (844 mg, 97% yield) was obtained.

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<sup>1</sup>H-NMR (400 MHz, DMSO-d<sub>6</sub>) δ ppm: 7.8 (d, 1 H), 7.5 (d, 1 H), 7.4 (dd, 1 H), 7.3 (dd, 1 H), 7.2 (m, 4 H), 4.8 (m, 3 H), 4.3/4.15 (2d, 2 H), 4.25 (m, 2 H), 4/3.8 (2d, 2 H), 3.95 (q, 2 H), 3.2 (d, 2 H), 2.8/2.65 (s+2m, 5 H), 2.2 (sl, 3 H), 1 (t, 3 H)

**STEP 4 : Preparation of EXAMPLE 69**

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3-{5-[1-(3-{[6-(Aminomethyl)-2,2-dioxo-2*H*-1,2λ<sup>6</sup>,3-benzoxathiazin-3(4*H*)-yl]methyl}-4-methylphenyl)-3-ethoxy-3-oxopropyl]-4-methyl-1*H*-benzotriazol-1-yl}propanoic acid (1 eq., 830 mg, 1.13 mmol) was dissolved in DCM (340 mL), then TEA (5 eq., 574 mg, 0.791 mL, 5.67 mmol), 1*H*-benzotriazol-1-ol (1.5 eq., 256 mg, 1.7 mmol) and 3-[[[(ethylimino)methylidene]amino]-*N,N*-dimethylpropan-1-amine hydrochloride (1.5 eq., 326 mg, 1.7 mmol) were added. The reaction mixture was stirred at RT overnight. The mixture was concentrated to 50 mL, and was washed with aq. sat. NaHCO<sub>3</sub> and brine. The aq. phases were extracted with DCM. The combined organic phases were washed with 10% aq. citric acid solution, with water, then with brine. The organic layer was dried over MgSO<sub>4</sub>, filtered,

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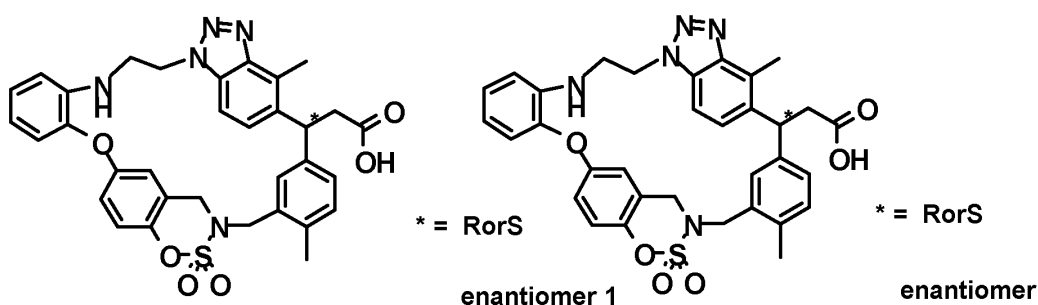
concentrated to give the crude ethyl [4,31-dimethyl-19,27,27-trioxo-26-oxa-27 $\lambda^6$ -thia-1,14,15,16,20-pentaazahexacyclo[20.5.3.1<sup>3,7</sup>.1<sup>9,13</sup>.0<sup>12,16</sup>.0<sup>25,29</sup>] dotriaconta-3(32),4,6,9(31),10,12,14,22,24,29-decaen-8-yl]acetate (53% yield), which was reacted using General Procedure 12 to give the title compound as a racemic mixture (45 mg, 13%).

5 **HRMS** calculated for C<sub>29</sub>H<sub>29</sub>N<sub>5</sub>O<sub>6</sub>S: 575.1838; [M+H]<sup>+</sup> found: 576.1913 ( $\delta$ =0.3 ppm)

**<sup>1</sup>H-NMR** (400 MHz, DMSO-d<sub>6</sub>)  $\delta$  ppm: 12.1 (m, 1 H), 8.35 (m, 1 H), 7.65/7.6 (d, 2 H), 7.45 (dd, 1 H), 7.25 (d+dd, 2 H), 7.1 (d, 1 H), 6.75 (d, 1 H), 6.3 (d, 1 H), 5.05/4.95 (m, 2 H), 4.8 (t, 1 H), 4.7/4 dd, 2 H), 4.3/3.9 (2d, 2 H), 4.1/3.7 (d, 2 H), 3/2.8 (m, 2 H), 3 (m, 2 H), 2.6 (s, 3 H), 2.3 (sl, 3 H)

10

**EXAMPLE 70** : [4,36-Dimethyl-32,32-dioxo-26,31-dioxa-32 $\lambda^6$ -thia-1,14,15,16,19-pentaazaheptacyclo[25.5.3.1<sup>3,7</sup>.1<sup>9,13</sup>.0<sup>12,16</sup>.0<sup>20,25</sup>.0<sup>30,34</sup>]heptatriaconta-3(37),4,6,9(36),10,12,14,20,22,24,27,29,34-tridecaen-8-yl]acetic acid



#### STEP C1 : Preparation of 1-(4-methoxyphenoxy)-2-nitrobenzene

4-Methoxyphenol (1 eq., 6.207 g, 50 mmol) and 1-fluoro-2-nitrobenzene (1 eq., 7.055 g, 0.05  
20 mol) were dissolved in dioxane (50 mL) and K<sub>2</sub>CO<sub>3</sub> (2 eq., 13.821 g, 0.1 mol) was added to the solution. The mixture was stirred at 100°C for 23h. After completion of the reaction the mixture was cooled to RT and the organic salts were filtered out. The filtrate was concentrated under reduced pressure and the residue was purified by trituration with heptane to afford the title compound (yellow crystals, 11.96 g, 98% yield).

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<sup>1</sup>H-NMR (500 MHz, DMSO-d<sub>6</sub>) δ ppm: 8.02 (dd, 1H), 7.63 (t, 1H), 7.29 (t, 1H), 7.07 (m, 2H), 7.00 (m, 3H), 3.76 (s, 3H)

**STEP C2 : Preparation of 4-(2-nitrophenoxy)phenol**

5

1-(4-Methoxyphenoxy)-2-nitrobenzene (1 eq., 11.96 g, 0.04878 mol) was dissolved in DCM (300 mL, 4.680 mol) at 0 °C. The solution of tribromoborane (1.2 eq., 14.66 g, 0.05853 mol) in 20 mL DCM was added dropwise. The reaction mixture was stirred overnight at RT. The mixture was poured into water (100 mL). The organic layer was washed with brine, dried over MgSO<sub>4</sub>,  
10 filtered and concentrated under reduced pressure. The residue was diluted with EtOAc and was purified by normal phase silica gel chromatography using heptane-EtOAc (100:0 to 66:33) as an eluent to give the title compound (11.11 g, yellow crystals, 98% yield).

<sup>1</sup>H-NMR (500 MHz, DMSO-d<sub>6</sub>) δ ppm: 9.52 (s, 1H), 7.99 (dd, 1H), 7.61 (m, 1H), 7.24 (t, 1H), 6.96 (m, 3H), 6.82 (m, 2H)

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**STEP C3 : Preparation of 2-hydroxy-5-(2-nitrophenoxy)benzaldehyde**

4-(2-Nitrophenoxy)phenol (1 eq., 11.11 g, 0.04805 mol) was dissolved in 1,2-dichloroethane (150 mL), then magnesium dichloride (5 eq., 22.88g, 0.2403 mol) and TEA (6 eq., 29.18 g, 0.2883 mol, 40.19mL) were added. Paraformaldehyde (10 eq., 14.42 g, 0.4805 mol) was added  
20 and the mixture was stirred at 40°C for an hour, then at 70°C for 12 h. The cooled mixture was diluted with DCM (300 mL) and washed with 3x50 mL 1M aq. HCl solution. The organic layer was dried over MgSO<sub>4</sub>, filtered and evaporated to give the title compound as brownish crystals (11.89 g, 95% yield).

25 <sup>1</sup>H-NMR (500 MHz, DMSO-d<sub>6</sub>) δ ppm: 10.8 (br., 1 H), 10.24 (s, 1 H), 8.04 (dd, 1 H), 7.66 (ddd, 1 H), 7.36 (dd, 1 H), 7.33 (td, 1 H), 7.27 (d, 1 H), 7.09 (d, 1 H), 7.09 (dd, 1 H)

**STEP C4 : Preparation of 6-(2-nitrophenoxy)-2H-1,2λ<sup>6</sup>,3-benzoxathiazine-2,2-dione**

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Chlorosulfonyl isocyanate (4 eq., 25.20 g, 15.50 mL, 0.1781 mol) was cooled to 0°C and HCOOH (4 eq., 8.196 g, 6.72 mL, 0.1781 mol) was added dropwise at 0°C over 30 minutes. A white precipitate was formed. The reaction mixture was allowed to warm to RT in 30 minutes and was stirred at RT for 1 h. The mixture was cooled again to 0°C and the solution of 2-hydroxy-5-(2-nitrophenoxy)benzaldehyde (1 eq., 11.54 g, 0.04452 mol) in NMP (75 mL) was added dropwise. The mixture was stirred overnight at RT. Pouring carefully into 100 mL cc. NH<sub>4</sub>Cl solution, an orange precipitate was formed, which after filtration and drying in vacuum gave the title compound as orange crystals (6.71 g, 47% yield).

<sup>1</sup>H-NMR (500 MHz, DMSO-d<sub>6</sub>) δ ppm: 9.15 (s, 1 H), 8.15 (dd, 1 H), 7.78 (td, 1 H), 7.71 (d, 1 H), 7.69 (dd, 1 H), 7.63 (d, 1 H), 7.48 (td, 1 H), 7.36 (dd, 1 H)

**STEP C5 : Preparation of 6-(2-nitrophenoxy)-3,4-dihydro-2H-1,2λ<sup>6</sup>,3-benzoxathiazine-2,2-dione**

6-(2-Nitrophenoxy)-2H-1,2λ<sup>6</sup>,3-benzoxathiazine-2,2-dione (1 eq., 7.65 g, 23.9 mmol) was dissolved in EtOH (250 mL) and sodium cyanoborohydride (1.2 eq., 1.8 g, 28.7 mmol) was added portionwise to the solution at 0°C. The mixture was stirred at RT for 30 min. The solvent was evaporated to dryness. The yellowish oil was partitioned between EtOAc and water. The organic layer was separated and the aqueous phase was extracted with EtOAc (2x30 mL). The combined organic phases were dried over MgSO<sub>4</sub>, filtered and concentrated. The residue was purified by normal phase flash chromatography on silica gel column with heptane-EtOAc (100:0 to 50:50) as an eluent to give the title compound as a yellowish oil (1.25 g, 16% yield).

<sup>1</sup>H-NMR (500 MHz, DMSO-d<sub>6</sub>) δ ppm: 8.54 (t, 1 H), 8.08 (dm, 1 H), 7.71 (m, 1 H), 7.39 (m, 1 H), 7.18 (dm, 1 H), 7.16 (d, 1 H), 7.09 (dd, 1 H), 7.07 (d, 1 H), 4.55 (d, 2 H)

**STEP A1 : Preparation of ethyl (2E)-3-(4-methyl-1-{2-[(oxan-2-yl)oxy]ethyl}-1H-benzotriazol-5-yl)prop-2-enoate**

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To a solution of 6-(2-nitrophenoxy)-3,4-dihydro-2*H*-1,2λ<sup>6</sup>,3-benzoxathiazine-2,2-dione (1 eq., 1.38 g, 5 mmol) in DCM (25 mL) at 0 °C 4-methylbenzene-1-sulfonic acid monohydrate (0.01 eq., 9.5 mg, 0.05 mmol) was added followed by addition of 3,4-dihydro-2*H*-pyran (1.1 equiv., 0.463 g, 5.5 mmol). The reaction mixture was allowed to warm to RT and stirred for 1 h. The mixture was quenched with saturated NaHCO<sub>3</sub> (30 mL) and the phases were separated. The aq. phase was extracted with DCM (30 mL), and the combined organic phases were dried over MgSO<sub>4</sub>, filtered and evaporated under reduced pressure to give the title compound (1.7 g, 95% yield).

<sup>1</sup>H-NMR (500 MHz, DMSO-d<sub>6</sub>) δ ppm: 8.01 (d, 1 H), 7.96 (d, 1 H), 7.72 (d, 1 H), 6.64 (d, 1 H), 4.93/4.88 (m+m, 2 H), 4.53 (dd, 1 H), 4.21 (q, 2 H), 4.05/3.84 (m+m, 2 H), 3.36/3.29 (m+m, 2 H), 2.8 (s, 3 H), 1.58-1.19 (m, 6 H), 1.27 (t, 3 H)

**STEP 1 : Preparation of 3-[3-(hydroxymethyl)-4-methylphenyl]-3-(4-methyl-1-{2-[(oxan-2-yl)oxy]ethyl}-1*H*-benzotriazol-5-yl)propanoic acid**

The suspension of ethyl (2*E*)-3-(4-methyl-1-{2-[(oxan-2-yl)oxy]ethyl}-1*H*-benzotriazol-5-yl)prop-2-enoate (1 eq., 4.85 g, 13.5 mmol) in dioxane (80 mL) and water (40 mL) was degassed with N<sub>2</sub>, then [2-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]methanol (1.4 eq., 4.69 g, 18.9 mmol) and TEA (1.6 eq., 2.18 g, 21.6 mmol) were added. Chloro(1,5-cyclooctadiene)rhodium(I) dimer catalyst (0.05 eq., 0.333 g, 0.675 mmol) was added and the reaction mixture was heated at 80 °C for 30 min, then at RT overnight. The reaction mixture was diluted with water and EtOAc, the organic phase was separated, dried over MgSO<sub>4</sub>, filtered and concentrated to dryness to give the crude product, which was purified via normal phase silica gel chromatography using heptane-EtOAc (50:50) as an eluent to give the title compound (dark oil, 5.11 g, 79% yield).

<sup>1</sup>H-NMR (500 MHz, DMSO-d<sub>6</sub>) δ ppm: 7.62 (d, 1 H), 7.47 (d, 1 H), 7.25 (brs., 1 H), 7.09/7.07 (dd/dd, 1 H), 7.02/7.01 (d/d, 1 H), 4.99/4.98 (t/t, 1 H), 4.9-4.78 (m, 2 H), 4.83 (m, 1 H), 4.51 (dm, 1 H), 4.4 (d, 2 H), 4.01/3.82 (m+m, 2 H), 3.92 (q, 2 H), 3.33-3.2 (m, 2 H), 3.13 (d, 2 H), 2.74 (s, 3 H), 2.15 (s, 3 H), 1.54-1.18 (m, 6 H), 1 (t, 3 H)

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**STEP 2 : Preparation of ethyl 3-(4-methyl-3-{[6-(2-nitrophenoxy)-2,2-dioxo-2*H*-1,2λ<sup>6</sup>,3-benzoxathiazin-3(4*H*)-yl]methyl}phenyl)-3-(4-methyl-1-{2-[(oxan-2-yl)oxy]ethyl}-1*H*-benzotriazol-5-yl)propanoate**

5 3-[3-(Hydroxymethyl)-4-methylphenyl]-3-(4-methyl-1-{2-[(oxan-2-yl)oxy]ethyl}-1*H*-benzotriazol-5-yl)propanoic acid (1 eq., 3.277 g, 6.804 mmol) was dissolved in THF (30 mL). To this solution 6-(2-nitrophenoxy)-3,4-dihydro-2*H*-1,2λ<sup>6</sup>,3-benzoxathiazine-2,2-dione (1.39 eq., 3.04 g, 9.43 mmol) dissolved in THF (10 mL) and PPh<sub>3</sub> (2 eq., 3.570 g, 13.61 mmol) were added. The mixture was cooled to ~5°C, DIAD (2 eq., 2.897 g, 2.821 mL, 13.61 mmol) was  
 10 added dropwise and the mixture was heated at 45 °C for 1h. The reaction mixture was concentrated to dryness to give the crude product, which was purified via normal phase silica gel chromatography using DCM-MeOH (99:1) as an eluent to give the title compound (orange solid, 5.3 g, 99% yield).

<sup>1</sup>**H-NMR** (500 MHz, DMSO-d<sub>6</sub>) δ ppm: 8.09 (dd, 1 H), 7.72 (td, 1 H), 7.58 (d, 1 H), 7.48 (d, 1 H), 7.38 (t, 1 H), 7.27 (dd, 1 H), 7.25 (m, 1 H), 7.24 (dm, 1 H), 7.17 (d, 1 H), 7.16 (m, 1 H),  
 15 7.12 (d, 1 H), 7.11 (m, 1 H), 4.82 (m, 1 H), 4.82 (m, 2 H), 4.48 (m, 2 H), 4.48 (m, 1 H), 4.26/4.23 (d+d, 2 H), 3.99/3.8 (m+m, 2 H), 3.89 (q, 2 H), 3.23 (m, 2 H), 3.15 (d, 2 H), 2.73/2.72 (s/s, 3 H), 2.22 (s, 3 H), 1.5-1.13 (m, 6 H), 0.97 (t, 3 H)

20 **STEP 3 : Preparation of ethyl 3-[1-(2-hydroxyethyl)-4-methyl-1*H*-benzotriazol-5-yl]-3-(4-methyl-3-{[6-(2-nitrophenoxy)-2,2-dioxo-2*H*-1,2λ<sup>6</sup>,3-benzoxathiazin-3(4*H*)-yl]methyl}phenyl)propanoate**

Ethyl 3-(4-methyl-3-{[6-(2-nitrophenoxy)-2,2-dioxo-2*H*-1,2λ<sup>6</sup>,3-benzoxathiazin-3(4*H*)-  
 25 yl]methyl}phenyl)-3-(4-methyl-1-{2-[(oxan-2-yl)oxy]ethyl}-1*H*-benzotriazol-5-yl)propanoate (1 eq., 3.091 g, 3.933 mmol) was dissolved in THF (16 mL) and EtOH (2 mL). Phosphotungstic acid hydrate (0.1 eq., 0.1368 g, 0.3933 mmol) was added and the reaction mixture was stirred at RT for 24 h. After completion of the reaction the mixture was concentrated to dryness. The crude solid product was partitioned between EtOAc and water. The separated organic layer was



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washed twice with sodium bicarbonate solution, dried over  $\text{MgSO}_4$ , filtered and evaporated to dryness to give the title compound (brown solid, 2.8 g, quant.).

**$^1\text{H-NMR}$**  (500 MHz,  $\text{DMSO-d}_6$ )  $\delta$  ppm: 8.09 (dd, 1 H), 7.71 (td, 1 H), 7.53 (d, 1 H), 7.45 (d, 1 H), 7.38 (td, 1 H), 7.27 (d, 1 H), 7.27 (d, 1 H), 7.24 (dd, 1 H), 7.18 (dd, 1 H), 7.17 (dd, 1 H),  
5 7.12 (d, 1 H), 7.12 (d, 1 H), 4.94 (t, 1 H), 4.83 (t, 1 H), 4.64 (t, 2 H), 4.48 (s, 2 H), 4.26 (s, 2 H), 3.91 (q, 2 H), 3.81 (q, 2 H), 3.15 (m, 2 H), 2.74 (s, 3 H), 2.22 (s, 3 H), 1 (t, 3 H)

**STEP 4 : Preparation of ethyl 3-[1-(2-chloroethyl)-4-methyl-1*H*-benzotriazol-5-yl]-3-(4-methyl-3-[[6-(2-nitrophenoxy)-2,2-dioxo-2*H*-1,2 $\lambda^6$ ,3-benzoxathiazin-3(4*H*)-yl]methyl}phenyl)propanoate**  
10

Ethyl 3-[1-(2-hydroxyethyl)-4-methyl-1*H*-benzotriazol-5-yl]-3-(4-methyl-3-[[6-(2-nitrophenoxy)-2,2-dioxo-2*H*-1,2 $\lambda^6$ ,3-benzoxathiazin-3(4*H*)-yl]methyl}phenyl)propanoate (1 eq., 2.8 g, 4.0 mmol) was dissolved in DCM (30 mL). Thionyl chloride (3 eq., 1.4 g, 12 mmol)  
15 was added slowly at RT. The reaction mixture was heated at 45 °C for 1.5h. After completion of the reaction the mixture was concentrated to dryness. The crude product was partitioned between EtOAc and water, the organic phase was washed twice with sat. aq. sodium bicarbonate solution, dried over  $\text{MgSO}_4$ , filtered and evaporated to dryness to give the title compound (2.9 g, brown solid, 97% yield).

**$^1\text{H-NMR}$**  (500 MHz,  $\text{DMSO-d}_6$ )  $\delta$  ppm: 8.09 (dm, 1 H), 7.71 (m, 1 H), 7.62 (d, 1 H), 7.5 (d, 1 H), 7.38 (m, 1 H), 7.28 (d, 1 H), 7.27 (d, 1 H), 7.24 (dm, 1 H), 7.19 (dd, 1 H), 7.18 (dd, 1 H),  
20 7.13 (d, 1 H), 7.11 (d, 1 H), 4.99 (t, 2 H), 4.83 (t, 1 H), 4.48 (s, 2 H), 4.26 (s, 2 H), 4.12 (t, 2 H), 3.9 (q, 2 H), 3.16 (d, 2 H), 2.76 (s, 3 H), 2.23 (s, 3 H), 0.97 (t, 3 H)

**STEP 5 : Preparation of ethyl 3-(3-[[6-(2-aminophenoxy)-2,2-dioxo-2*H*-1,2 $\lambda^6$ ,3-benzoxathiazin-3(4*H*)-yl]methyl]-4-methylphenyl)-3-[1-(2-chloroethyl)-4-methyl-1*H*-benzotriazol-5-yl]propanoate**  
25

The mixture of ethyl 3-[1-(2-chloroethyl)-4-methyl-1*H*-benzotriazol-5-yl]-3-(4-methyl-3-[[6-(2-nitrophenoxy)-2,2-dioxo-2*H*-1,2 $\lambda^6$ ,3-benzoxathiazin-3(4*H*)-yl]methyl}phenyl)propanoate  
30

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(1 eq., 2.78 g, 3.86 mmol), iron powder (10 eq., 2160 mg, 38.6 mmol) and NH<sub>4</sub>Cl (0.5 eq., 103 mg, 1.93 mmol), dissolved in EtOH (10 mL) and water (3 mL) was heated at 80 °C for 1.5h. After cooling to RT, the mixture was filtered and concentrated under reduced pressure. The residue was dissolved in EtOAc, washed with sat. aq. Na<sub>2</sub>CO<sub>3</sub> solution, dried over MgSO<sub>4</sub>,  
 5 filtered, evaporated under reduced pressure, and dried in *vacuo* overnight to give the title compound (2.314 g, brown solid, 87% yield).

<sup>1</sup>H-NMR (500 MHz, DMSO-d<sub>6</sub>) δ ppm: 7.63 (d, 1 H), 7.52 (d, 1 H), 7.25 (d, 1 H), 7.18 (dd, 1 H), 7.16 (d, 1 H), 7.12 (d, 1 H), 6.93 (m, 1 H), 6.92 (dd, 1 H), 6.85 (d, 1 H), 6.84 (dm, 1 H), 6.81 (dm, 1 H), 6.56 (m, 1 H), 5 (t, 2 H), 4.97 (s, 2 H), 4.83 (t, 1 H), 4.45 (s, 2 H), 4.23 (s, 2  
 10 H), 4.13 (t, 2 H), 3.91 (q, 2 H), 3.16 (d, 2 H), 2.76 (s, 3 H), 2.22 (s, 3 H), 0.99 (t, 3 H)

**STEP 6 : Preparation of ethyl [4,36-dimethyl-32,32-dioxo-26,31-dioxa-32λ<sup>6</sup>-thia-1,14,15,16,19-**

**pentaazaheptacyclo[25.5.3.1<sup>3,7</sup>.1<sup>9,13</sup>.0<sup>12,16</sup>.0<sup>20,25</sup>.0<sup>30,34</sup>]heptatriaconta-**  
 15 **3(37),4,6,9(36),10,12,14,20,22,24,27,29,34-tridecaen-8-yl]acetate**

Ethyl 3-(3-{[6-(2-aminophenoxy)-2,2-dioxo-2*H*-1,2λ<sup>6</sup>,3-benzoxathiazin-3(4*H*)-yl]methyl}-4-methylphenyl)-3-[1-(2-chloroethyl)-4-methyl-1*H*-benzotriazol-5-yl]propanoate (1 eq., 1.12 g, 1.62 mmol) was dissolved in propanenitrile (50 mL) and sodium iodide (5 eq., 1.22 g, 8.11  
 20 mmol) was added at RT. The reaction mixture was heated at 100 °C for 35 h. The mixture was concentrated to dryness then partitioned between water and EtOAc. The organic phase was separated and dried over MgSO<sub>4</sub>, filtered and concentrated to dryness to give the crude product, which was purified via preparative reversed-phase chromatography using aq. TFA solution-MeCN as eluents to give the title compound (360 mg, yellow powder, 34% yield).

25 The enantiopure final intermediates were obtained by chromatographic separation on chiral column.

<sup>1</sup>H-NMR (500 MHz, DMSO-d<sub>6</sub>) δ ppm: 7.39 (d, 1 H), 7.37 (dd, 1 H), 7.34 (d, 1 H), 7.21 (d, 1 H), 7.16 (d, 1 H), 7.06 (dd, 1 H), 7 (t, 1 H), 6.9 (d, 1 H), 6.86 (d, 1 H), 6.69 (d, 1 H), 6.56 (t, 1 H), 6.37 (d, 1 H), 5.47 (dd, 1 H), 4.95/4.83 (dt+dt, 2 H), 4.8 (t, 1 H), 4.27/4.1 (d+d, 2 H),

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4.21/4.15 (d+d, 2 H), 3.87 (q, 2 H), 3.79/3.68 (m+m, 2 H), 3.08/2.99 (dd+dd, 2 H), 2.7 (s, 3 H), 2.3 (s, 3 H), 0.95 (t, 3 H)

#### STEP 7 : Preparation of EXAMPLE 70

5

Using General Procedure 12 starting from ethyl [4,36-dimethyl-32,32-dioxo-26,31-dioxa-32 $\lambda^6$ -thia-1,14,15,16,19-pentaazaheptacyclo[25.5.3.1<sup>3,7</sup>.1<sup>9,13</sup>.0<sup>12,16</sup>.0<sup>20,25</sup>.0<sup>30,34</sup>]heptatriaconta-3(37),4,6,9(36),10,12,14,20,22,24,27,29,34-tridecaen-8-yl]acetate E1 (1 eq.) or E2 (1 eq.) as reactants, the title compounds (58% - 92% yields respectively) were obtained.

10

##### Example 70a (E1)

HRMS calculated for C<sub>33</sub>H<sub>31</sub>N<sub>5</sub>O<sub>6</sub>S: 625.1995; [M+H]<sup>+</sup> found: 626.2062 ( $\delta$  = -0.9 ppm)

##### Example 70b (E2)

15 HRMS calculated for C<sub>33</sub>H<sub>31</sub>N<sub>5</sub>O<sub>6</sub>S: 625.1995; [M+H]<sup>+</sup> found: 626.2062 ( $\delta$  = -0.9 ppm)

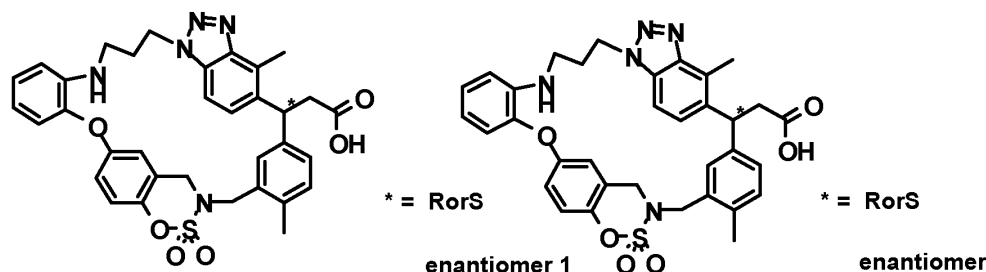
<sup>1</sup>H-NMR (500 MHz, DMSO-d<sub>6</sub>)  $\delta$  ppm: 12.07 (brs, 1 H), 7.38 (dd, 1 H), 7.38 (d, 1 H), 7.32 (d, 1 H), 7.21 (d, 1 H), 7.16 (d, 1 H), 7.06 (dd, 1 H), 7 (t, 1 H), 6.9 (d, 1 H), 6.84 (d, 1 H), 6.69 (d, 1 H), 6.56 (t, 1 H), 6.37 (d, 1 H), 5.47 (brs, 1 H), 4.95/4.82 (t+d, 2 H), 4.77 (t, 1 H), 4.27/4.09 (d+d, 2 H), 4.2/4.14 (d+d, 2 H), 3.79/3.68 (t+d, 2 H), 2.99/2.87 (dd+dd, 2 H), 2.7 (s, 3 H), 2.3 (s, 3 H)

20

<sup>13</sup>C-NMR (125 MHz, DMSO-d<sub>6</sub>)  $\delta$  ppm: 173.1, 155, 146.3, 146.2, 143.8, 141.6, 140.2, 136.4, 136.1, 133.1, 132.1, 131.4, 130.2, 129, 127.2, 127.1, 125.4, 120.1, 119.7, 119.3, 118.6, 117, 116.1, 111.8, 108.1, 51.9, 48.8, 47.6, 44.3, 41.2, 41.2, 18.6, 13.3

25 EXAMPLE 71 : [4,37-Dimethyl-33,33-dioxo-27,32-dioxa-33 $\lambda^6$ -thia-1,14,15,16,20-pentaazaheptacyclo[26.5.3.1<sup>3,7</sup>.1<sup>9,13</sup>.0<sup>12,16</sup>.0<sup>21,26</sup>.0<sup>31,35</sup>]octatriaconta-3(38),4,6,9(37),10,12,14,21,23,25,28,30,35-tridecaen-8-yl]acetic acid

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**STEP 1 : Preparation of ethyl 3-[4-methyl-3-[[6-(2-nitrophenoxy)-2,2-dioxo-4H-1,2λ6,3-benzoxathiazin-3-yl]methyl]phenyl]-3-[4-methyl-1-(3-tetrahydropyran-2-yloxypropyl)benzotriazol-5-yl]propanoate**

Ethyl 3-[3-(hydroxymethyl)-4-methylphenyl]-3-(4-methyl-1-{3-[(oxan-2-yl)oxy]propyl}-1*H*-benzotriazol-5-yl)propanoate (1 eq., 1890 mg, 3.81 mmol) was dissolved in THF (25 mL), then 6-(2-nitrophenoxy)-3,4-dihydro-2*H*-1,2λ<sup>6</sup>,3-benzoxathiazine-2,2-dione (1.5 eq., 1.8 g, 5.58 mmol) and PPh<sub>3</sub> (3.2 eq., 3.2 g, 12.2 mmol) were added. The mixture was cooled to 5 °C under inert atmosphere (N<sub>2</sub>) and DIAD (3.11 eq., 2.4 g, 11.9 mmol) was added dropwise. The reaction mixture was stirred at RT for 2h. After completion of the reaction the solvent was evaporated under reduced pressure, the crude product was purified by normal phase flash chromatography on silica gel with heptane-EtOAc (50:50) as eluents to obtain the title compound as yellowish solid (2.04 g, 67% yield).

**<sup>1</sup>H-NMR** (500 MHz, DMSO-d<sub>6</sub>) δ ppm: 8.09 (dd, 1 H), 7.71 (td, 1 H), 7.54 (d, 1 H), 7.48 (d, 1 H), 7.42 (m, 1 H), 7.38 (td, 1 H), 7.27 (d, 1 H), 7.25 (d, 1 H), 7.24 (dd, 1 H), 7.18 (dd, 1 H), 7.18 (dd, 1 H), 7.12 (d, 1 H), 7.1 (d, 1 H), 4.83 (t, 1 H), 4.68 (t, 2 H), 4.47 (s, 2 H), 4.25 (s, 2 H), 3.9 (q, 2 H), 3.6/3.31 (m+m, 2 H), 3.57/3.24 (m+m, 2 H), 3.15 (d, 2 H), 2.74 (s, 3 H), 2.23 (s, 3 H), 2.11 (m, 2 H), 1.67-1.29 (m, 6 H), 0.98 (t, 3 H)

**STEP 2 : Preparation of ethyl 3-[1-(3-hydroxypropyl)-4-methyl-1*H*-benzotriazol-5-yl]-3-(4-methyl-3-{[6-(2-nitrophenoxy)-2,2-dioxo-2*H*-1,2λ<sup>6</sup>,3-benzoxathiazin-3(4*H*)-yl]methyl}phenyl)propanoate**

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Ethyl 3-[4-methyl-3-[[6-(2-nitrophenoxy)-2,2-dioxo-4H-1,2λ<sup>6</sup>,3-benzoxathiazin-3-yl]methyl]phenyl]-3-[4-methyl-1-(3-tetrahydropyran-2-yloxypropyl)benzotriazol-5-yl]propanoate (1 eq., 2.03 g, 2.54 mmol) was dissolved in EtOH (40 mL) and THF (25 mL), then pyridinium *p*-toluenesulfonate (0.1 eq., 64 mg, 0.127 mmol) was added to the solution. The reaction mixture was stirred at 55 °C overnight. After completion of the reaction, the solvents were evaporated, the mixture was diluted with DCM and washed with sat. aq. NaHCO<sub>3</sub>. The layers were separated, the organic layer was dried over MgSO<sub>4</sub>. After filtration the filtrate was concentrated to obtain the title compound as white solid (1.8 g, quant.).

<sup>1</sup>H-NMR (500 MHz, DMSO-d<sub>6</sub>) δ ppm: 8.09 (dd, 1 H), 7.71 (td, 1 H), 7.54 (d, 1 H), 7.47 (d, 1 H), 7.38 (td, 1 H), 7.27 (d, 1 H), 7.25 (d, 1 H), 7.24 (dd, 1 H), 7.18 (dd, 1 H), 7.18 (dd, 1 H), 7.12 (d, 1 H), 7.1 (d, 1 H), 4.82 (t, 1 H), 4.65 (t, 1 H), 4.65 (m, 2 H), 4.47 (s, 2 H), 4.25 (s, 2 H), 3.9 (q, 2 H), 3.35 (q, 2 H), 3.15 (m, 2 H), 2.74 (s, 3 H), 2.23 (s, 3 H), 1.98 (m, 2 H), 0.98 (t, 3 H)

**STEP 3 : Preparation of ethyl 3-[1-(3-chloropropyl)-4-methyl-1H-benzotriazol-5-yl]-3-(4-methyl-3-[[6-(2-nitrophenoxy)-2,2-dioxo-2H-1,2λ<sup>6</sup>,3-benzoxathiazin-3(4H)-yl]methyl]phenyl)propanoate**

Using General Procedure 10 starting from ethyl 3-[1-(3-hydroxypropyl)-4-methyl-1H-benzotriazol-5-yl]-3-(4-methyl-3-[[6-(2-nitrophenoxy)-2,2-dioxo-2H-1,2λ<sup>6</sup>,3-benzoxathiazin-3(4H)-yl]methyl]phenyl)propanoate (1 eq., 1.8 g, 2.5 mmol) as a reactant, the title compound (1.8 g, quant., brown oil) was obtained.

<sup>1</sup>H-NMR (500 MHz, DMSO-d<sub>6</sub>) δ ppm: 8.09 (dd, 1 H), 7.71 (td, 1 H), 7.56 (d, 1 H), 7.5 (d, 1 H), 7.38 (td, 1 H), 7.27 (d, 1 H), 7.27 (d, 1 H), 7.24 (dd, 1 H), 7.18 (dd, 1 H), 7.18 (dd, 1 H), 7.13 (d, 1 H), 7.1 (d, 1 H), 4.82 (t, 1 H), 4.74 (t, 2 H), 4.48 (s, 2 H), 4.26 (s, 2 H), 3.9 (q, 2 H), 3.58 (t, 2 H), 3.15 (d, 2 H), 2.75 (s, 3 H), 2.31 (quint., 2 H), 2.23 (s, 3 H), 0.98 (t, 3 H)

**STEP 4 : Preparation of ethyl 3-(3-[[6-(2-aminophenoxy)-2,2-dioxo-2H-1,2λ<sup>6</sup>,3-benzoxathiazin-3(4H)-yl]methyl]-4-methylphenyl)-3-[1-(3-chloropropyl)-4-methyl-1H-benzotriazol-5-yl]propanoate**

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Using General Procedure 1 STEP 3 starting from ethyl 3-[1-(3-chloropropyl)-4-methyl-1*H*-benzotriazol-5-yl]-3-(4-methyl-3-{{[6-(2-nitrophenoxy)-2,2-dioxo-2*H*-1,2λ<sup>6</sup>,3-benzoxathiazin-3(4*H*)-yl]methyl} phenyl)propanoate (1 eq., 1.8 g, 2.5 mmol) as a reactant, the title compound  
5 (1.41 g, 82% yield, brown solid) was obtained.

**HRMS** calculated for C<sub>36</sub>H<sub>38</sub>ClN<sub>5</sub>O<sub>6</sub>S: 703.2231; [M+H]<sup>+</sup> found: 704.2301 (δ = -0.4 ppm)

**STEP 5 : Preparation of ethyl [4,37-dimethyl-33,33-dioxo-27,32-dioxa-33λ<sup>6</sup>-thia-1,14,15,16,20-**  
10 **pentaazaheptacyclo[26.5.3.1<sup>3,7</sup>.1<sup>9,13</sup>.0<sup>12,16</sup>.0<sup>21,26</sup>.0<sup>31,35</sup>]octatriaconta-**  
**3(38),4,6,9(37),10,12,14,21,23,25,28,30,35-tridecaen-8-yl]acetate**

Ethyl 3-(3-{{[6-(2-aminophenoxy)-2,2-dioxo-2*H*-1,2λ<sup>6</sup>,3-benzoxathiazin-3(4*H*)-yl]methyl}-4-methylphenyl)-3-[1-(3-chloropropyl)-4-methyl-1*H*-benzotriazol-5-yl]propanoate (1 eq., 500  
15 mg, 0.7100 mmol) was dissolved in propanenitrile (25 mL) and sodium iodide (2 eq., 213 mg, 1.420 mmol) was added at RT. The mixture was heated to 100 °C and refluxed for 5 h. K<sub>2</sub>CO<sub>3</sub> (2 eq., 196 mg, 1.420 mmol) was added and the mixture was stirred at 100°C for 6h. The solvent was evaporated under reduced pressure and the residue was partitioned between DCM and water. The organic layer was separated and washed with 1M aq. HCl solution, then with sat. aq.  
20 NaHCO<sub>3</sub> solution. The organic phase was dried over MgSO<sub>4</sub>, and after filtration evaporated under reduced pressure. The crude product was purified by reversed-phase chromatography using water-MeCN as eluents to give the title compound as white solid (125 mg, 0.187 mmol, 26% yield).

**<sup>1</sup>H-NMR** (500 MHz, DMSO-d<sub>6</sub>) δ ppm: 7.6 (d, 1 H), 7.4 (dd, 1 H), 7.36 (d, 1 H), 7.2 (d, 1 H),  
25 7.13 (d, 1 H), 7.04 (t, 1 H), 6.91 (d, 1 H), 6.89 (dd, 1 H), 6.88 (d, 1 H), 6.86 (d, 1 H), 6.85 (d, 1 H), 6.64 (t, 1 H), 5.05 (brt, 1 H), 4.85 (t, 1 H), 4.74/4.56 (dt+dt, 2 H), 4.29/4.11 (d+d, 2 H), 4.21/4.09 (d+d, 2 H), 3.9 (q, 2 H), 3.29/3.01 (m+m, 2 H), 3.16 (d, 2 H), 2.69 (s, 3 H), 2.27 (s, 3 H), 2.19 (qn, 2 H), 0.99 (t, 3 H)

30 **STEP 6 : Preparation of EXAMPLE 71**

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Using General Procedure 12 starting from ethyl [4,37-dimethyl-33,33-dioxo-27,32-dioxa-33 $\lambda^6$ -thia-1,14,15,16,20-pentaazaheptacyclo[26.5.3.1<sup>3,7</sup>.1<sup>9,13</sup>.0<sup>12,16</sup>.0<sup>21,26</sup>.0<sup>31,35</sup>]octatriaconta-

3(38),4,6,9(37),10,12,14,21,23,25,28,30,35-tridecaen-8-yl]acetate (1 eq., 170 mg, 0.25 mmol)  
 5 as a reactant, the title compound (135 mg, 83% yield, white solid) was obtained.

The enantiopure products were obtained by ~~the~~ chromatographic separation on chiral column.

**Example 71a** (E1, optical purity: 97.9%)

HRMS calculated for C<sub>34</sub>H<sub>33</sub>N<sub>5</sub>O<sub>6</sub>S: 639.2151; [M+H]<sup>+</sup> found: 640.2231 ( $\delta$  = 1.0 ppm)

10

**Example 71b** (E2, optical purity>99.9%)

HRMS calculated for C<sub>34</sub>H<sub>33</sub>N<sub>5</sub>O<sub>6</sub>S: 639.2151; [M+H]<sup>+</sup> found: 640.2226 ( $\delta$  = 0.3 ppm)

<sup>1</sup>H-NMR (500 MHz, DMSO-d<sub>6</sub>)  $\delta$  ppm: 12.32 (brs, 1 H), 7.56 (d, 1 H), 7.39 (dd, 1 H), 7.34 (d, 1 H), 7.17 (d, 1 H), 7.12 (d, 1 H), 7.04 (t, 1 H), 6.88 (dd, 1 H), 6.87 (d, 1 H), 6.86 (d, 1 H), 6.85  
 15 (d, 1 H), 6.82 (d, 1 H), 6.63 (t, 1 H), 5.04 (t, 1 H), 4.84 (t, 1 H), 4.73/4.55 (dt+dt, 2 H), 4.28/4.14 (d+d, 2 H), 4.2/4.09 (d+d, 2 H), 3.28/3.02 (m+m, 2 H), 2.96 (m, 2 H), 2.68 (s, 3 H), 2.27 (s, 3 H), 2.19 (qn, 2 H)

<sup>13</sup>C-NMR (125 MHz, DMSO-d<sub>6</sub>)  $\delta$  ppm: 154.7, 146.5, 146.1, 143.1, 142.4, 140.4, 137, 135.7, 132, 131.7, 131.3, 129.8, 129.3, 127.7, 127.3, 126, 120.1, 119.5, 118.9, 118.1, 117.2, 116.7,  
 20 113, 107.3, 51.5, 49.1, 45, 42.5, 41.6, 39.6, 28.3, 18.4, 13.3

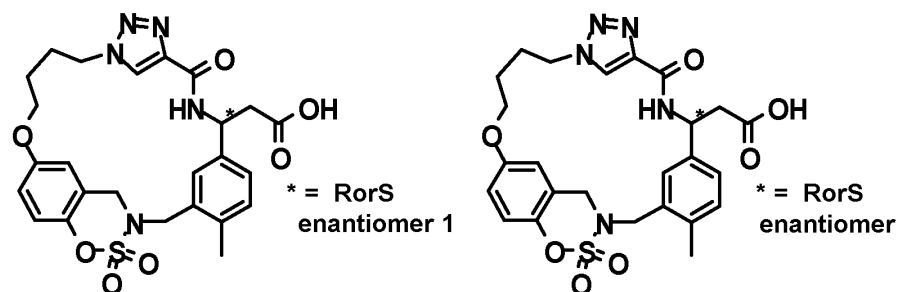
**EXAMPLE 72** : [4-Methyl-10,25,25-trioxo-19,24-dioxa-25 $\lambda^6$ -thia-1,9,12,13,14-

pentaazapentacyclo[18.5.3.1<sup>3,7</sup>.1<sup>11,14</sup>.0<sup>23,27</sup>]triaconta-

3(30),4,6,11(29),12,20,22,27-octaen-8-yl]acetic acid

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### STEP 1 : Preparation of [(5-bromo-2-methylphenyl)methoxy](*tert*-butyl)diphenylsilane

5 A mixture of (5-bromo-2-methylphenyl)methanol (1 eq., 20 g, 99 mmol), imidazole (3 eq., 20 g, 297 mmol) and DCM (250 mL) was stirred at 10 °C. *Tert*-butyl(chloro)diphenylsilane was added and the mixture was stirred for 1h at this temperature. After completion of the reaction, the mixture was quenched with water (300 mL), the resulted mixture was extracted with DCM, the layers were separated. The organic layer was dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>, filtered and the

10 filtrate was evaporated under reduced pressure. The crude product was purified by normal phase silica gel chromatography using heptane-DCM (100:0 to 50:50) as eluents. The title compound was obtained as colorless solid (44 g, quant.).

<sup>1</sup>H-NMR (400 MHz, DMSO-d<sub>6</sub>) δ ppm: 7.63 (m, 4 H), 7.55 (d, 1 H), 7.44 (m, 6 H), 7.37 (dd, 1 H), 7.11 (d, 1 H), 4.73 (s, 2 H), 2.09 (s, 3 H), 1.04 (s, 9 H)

15

### STEP 2 : Preparation of 1-[3-({[*tert*-butyl(diphenyl)silyl]oxy}methyl)-4-methylphenyl]ethan-1-one

To a stirred solution of [(5-bromo-2-methylphenyl)methoxy](*tert*-butyl)diphenylsilane (1 eq., 20 g, 45.5 mmol) in THF (364 mL, 8 mL/ mmol) butyllithium (2.6 M, 2 eq., 35 mL, 91 mmol) was added dropwise at -78 °C under inert atmosphere and the mixture was stirred overnight at this temperature. N,N-dimethylacetamide (3 eq., 14.1 g, 137 mmol) was added dropwise at -78 °C and the mixture was stirred for additional 1h at -78 °C. The mixture was allowed to warm to RT and stirred overnight. After completion of the reaction, the mixture was quenched with

20



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water, extracted with EtOAc, the layers were separated. The organic layer was dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and the filtrate was evaporated under reduced pressure. The crude product was purified by normal phase silica gel chromatography using heptane-EtOAc-EtOH (100:0:0 to 70:22.5:7.5) as eluents. The title compound was obtained as a colorless solid (9.5 g, 47% yield).

5 <sup>1</sup>H-NMR (400 MHz, CDCl<sub>3</sub>) δ ppm: 8.1 (d, 1 H), 7.8 (dd, 1 H), 7.7 (dd, 4 H), 7.4 (td+d, 6 H), 7.2 (d, 1 H), 4.8 (s, 2 H), 2.6 (s, 3 H), 2.2 (s, 3 H), 1.1 (q, 9 H)

**STEP 3 : Preparation of methyl 3-[3-([*tert*-butyl(diphenyl)silyl]oxy)methyl]-4-methylphenyl]-3-oxopropanoate**

10

To a stirred solution of 1-[3-([*tert*-butyl(diphenyl)silyl]oxy)methyl]-4-methylphenyl]ethan-1-one (1 eq., 9.5 g, 23.6 mmol) in dimethyl carbonate (11 eq., 23.4 g, 259.6 mmol) NaH (2 eq., 1.88 g, 12 mmol, 47.2 mmol, 60 wt% in mineral oil) was added at RT. The mixture was heated at 95 °C for 4h. After completion of the reaction, the mixture was cooled to RT, diluted with

15 water, the resulted mixture was extracted with EtOAc. The layers were separated, the organic layer was dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and the filtrate was evaporated under reduced pressure. The crude product was purified by normal phase silica gel chromatography using heptane-DCM (100:0 to 0:100) as eluents. The title compound was obtained as a colorless oil (7.9 g, 73% yield).

20 <sup>1</sup>H-NMR (400 MHz, DMSO-d<sub>6</sub>) δ ppm: 8.05 (d, 1 H), 7.8 (dd, 1 H), 7.65 (m, 4 H), 7.51-7.4 (m, 6 H), 7.33 (d, 1 H), 4.8 (s, 2 H), 4.13 (s, 2 H), 3.64 (s, 3 H), 2.22 (s, 3 H), 1.05 (s, 9 H)

**STEP 4 : Preparation of methyl 3-amino-3-[3-([*tert*-butyl(diphenyl)silyl]oxy)methyl]-4-methylphenyl]propanoate**

25

The mixture of methyl 3-[3-([*tert*-butyl(diphenyl)silyl]oxy)methyl]-4-methylphenyl]-3-oxopropanoate (1 eq., 7.9 g, 17 mmol), ammonium acetate (5 eq., 6.6 g, 86 mmol) and MeOH (86 mL, 5 mL/mmol) was stirred at reflux temperature overnight. After completion of the reaction, the solvent was evaporated under reduced pressure to give methyl 3-[3-([*tert*-

30 butyl(diphenyl)silyl]oxy)methyl]-4-methylphenyl]-3-iminopropanoate as an oil. The crude

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product was dissolved in AcOH (43 mL, 2.5 mL/mmol) and sodium borohydride was added slowly to the mixture at 10 °C. The mixture was allowed to warm to RT and stirred overnight. The mixture was quenched with sat. aq. K<sub>2</sub>CO<sub>3</sub> solution, the resulted mixture was extracted with EtOAc. The layers were separated, the organic layer was dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and the  
5 filtrate was evaporated under reduced pressure. The crude product was used in a next step without further purification (7.4 g oil, 75% yield).

<sup>1</sup>H-NMR (400 MHz, DMSO-d<sub>6</sub>) δ ppm: 7.65 (dd, 4 H), 7.4 (m, 7 H), 7.2 (dd, 1 H), 7.1 (d, 1 H), 4.7 (s, 2 H), 4.25 (m, 1 H), 3.55 (s, 3 H), 2.65 (2dd, 2 H), 2.15 (s, 3 H), 1 (s, 9 H)

10 **STEP 5 : Preparation of methyl 3-[(*tert*-butoxycarbonyl)amino]-3-[3-({*tert*-butyl(diphenyl)silyl}oxy)methyl)-4-methylphenyl]propanoate**

To a stirred solution of methyl 3-amino-3-[3-({*tert*-butyl(diphenyl)silyl}oxy)methyl)-4-methylphenyl]propanoate (1 eq., 4 g, 7.02 mmol) in DCM (56 mL, 8 mL/mmol) TEA (1.2 eq.,  
15 2.5 mL, 18 mmol) and di-*tert*-butyl-dicarbonate (1.2 eq., 1.84 g, 8.42 mmol) were added at RT. The mixture was stirred at RT for 4h. After completion of the reaction the mixture was diluted with water, then extracted with EtOAc. The organic layer was separated and dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>, filtered, concentrated to dryness. The crude product was purified by normal phase silica gel chromatography using heptane-EtOAc-EtOH (100:0:0 to 70:22.5:7.5) as  
20 eluents. The title compound was obtained as a colorless oil (3.7 g, 92% yield).

<sup>1</sup>H-NMR (400 MHz, DMSO-d<sub>6</sub>) δ ppm: 7.65 (m, 4 H), 7.4 (m, 9 H), 7.1 (dd+d, 2 H), 4.9 (m, 1 H), 4.7 (s, 2 H), 3.55 (s, 3 H), 2.7 (2dd, 2 H), 2.1 (s, 3 H), 1.3 (m, 9 H), 1 (s, 9 H)

25 **STEP 6 : Preparation of methyl 3-[(*tert*-butoxycarbonyl)amino]-3-[3-(hydroxymethyl)-4-methylphenyl]propanoate**

The mixture of methyl 3-[(*tert*-butoxycarbonyl)amino]-3-[3-({*tert*-butyl(diphenyl)silyl}oxy)methyl)-4-methylphenyl]propanoate (1 eq., 16.4 g, 29.3 mmol), tetrabutylammonium fluoride (1 eq., 26.4 g, 29.3 mmol) and THF (234 mL, 8 mL/mmol) was stirred at RT for 1h.  
30 After completion of the reaction, the mixture was quenched with sat. aq. NaHCO<sub>3</sub> solution, the

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resulted mixture was extracted with EtOAc. The layers were separated, the organic layer was dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and evaporated under reduced pressure. The crude product was purified by normal phase silica gel chromatography using heptane-EtOAc (80:20 to 30:70) as eluents. The title compound was obtained as a colorless oil (8.55 g, 90% yield).

5 <sup>1</sup>H-NMR (400 MHz, DMSO-d<sub>6</sub>) δ ppm: 7.42 (d, 1 H), 7.29 (s, 1 H), 7.08-7.02 (m, 2 H), 5.05 (t, 1 H), 4.88 (m, 1 H), 4.45 (d, 2 H), 3.55 (s, 3 H), 2.73/2.62 (2dd, 2 H), 2.19 (s, 3 H), 1.35 (s, 9 H)

10 **STEP 7 : Preparation of methyl 3-(3-{[6-(benzyloxy)-2,2-dioxo-2*H*-1,2λ<sup>6</sup>,3-benzoxathiazin-3(4*H*)-yl]methyl}-4-methylphenyl)-3-[(*tert*-butoxycarbonyl)amino]propanoate**

Using General Procedure 7 starting from methyl 3-[(*tert*-butoxycarbonyl)amino]-3-[3-(hydroxymethyl)-4-methylphenyl]propanoate (1 eq.) and 6-(benzyloxy)-3,4-dihydro-2*H*-1,2λ<sup>6</sup>,3-benzoxathiazine-2,2-dione (1.1 eq.) as reactants, the title compound (9 g, 81% yield) was obtained.

15 <sup>1</sup>H-NMR (400 MHz, DMSO-d<sub>6</sub>) δ ppm: 7.45 (d, 1 H), 7.45 (d, 2 H), 7.42 (t, 2 H), 7.38 (t, 1 H), 7.2 (m, 3 H), 7.18 (d, 1 H), 7.1 (dd, 1 H), 7 (d, 1 H), 5.09 (s, 2 H), 4.9 (m, 1 H), 4.48 (s, 2 H), 4.22 (m, 2 H), 3.55 (s, 3 H), 2.76/2.7 (2dd, 2 H), 2.23 (s, 3 H), 1.38 (s, 9 H)

20

**STEP 8 : Preparation of methyl 3-(3-{[6-(4-bromobutoxy)-2,2-dioxo-2*H*-1,2λ<sup>6</sup>,3-benzoxathiazin-3(4*H*)-yl]methyl}-4-methylphenyl)-3-[(*tert*-butoxycarbonyl)amino]propanoate**

25 Using General Procedure 8 starting from methyl 3-(3-{[6-(benzyloxy)-2,2-dioxo-2*H*-1,2λ<sup>6</sup>,3-benzoxathiazin-3(4*H*)-yl]methyl}-4-methylphenyl)-3-[(*tert*-butoxycarbonyl)amino]propanoate (1 eq.) as a reactant, methyl 3-[(*tert*-butoxycarbonyl)amino]-3-{3-[(6-hydroxy-2,2-dioxo-2*H*-1,2λ<sup>6</sup>,3-benzoxathiazin-3(4*H*)-yl)methyl]-4-methylphenyl}propanoate (4.3 g, 62% yield) was obtained. To the solution of the crude product (0.5 g, 1 mmol, 7.35 mL) in MeCN  
30 (10 mL/mmol, 10 mL) 1,4-dibromobutane (1.5 eq., 0.2 mL, 46.5 mmol) and Cs<sub>2</sub>CO<sub>3</sub> (3 eq., 0.6

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g, 3 mmol) were added at RT and the mixture was stirred overnight. After completion of the reaction the solvent was evaporated. The crude product was purified by reversed-phase chromatography using water-MeCN gradient elution (59:41 to 5:95) to give the title compound (345 mg white solid, 50% yield).

- 5 <sup>1</sup>H-NMR (400 MHz, DMSO-d<sub>6</sub>) δ ppm: 7.45 (d, 1 H), 7.25-7.15 (m, 3 H), 7.11 (d, 1 H), 7 (dd, 1 H), 6.89 (d, 1 H), 4.88 (m, 1 H), 4.45/4.2 (s+m, 4 H), 4 (t, 2 H), 3.6 (t, 2 H), 3.55 (s, 3 H), 2.77/2.68 (2dd, 2 H), 2.22 (s, 3 H), 1.95 (m, 2 H), 1.8 (m, 2 H), 1.35 (s, 9 H)

10 **STEP 9 : Preparation of methyl 3-(3-{{6-(4-azidobutoxy)-2,2-dioxo-2H-1,2λ<sup>6</sup>,3-benzoxathiazin-3(4H)-yl}methyl}-4-methylphenyl)-3-[(tert-butoxycarbonyl)amino]propanoate**

The mixture of methyl 3-(3-{{6-(4-bromobutoxy)-2,2-dioxo-2H-1,2λ<sup>6</sup>,3-benzoxathiazin-3(4H)-yl}methyl}-4-methylphenyl)-3-[(tert-butoxycarbonyl)amino]propanoate (1 eq., 345 mg, 0.538 mmol), sodium azide (2.3 eq., 80 mg, 1.23 mmol) and DMF (10 mL) was stirred overnight at RT. After completion of the reaction, the mixture was quenched with ice cold water, the resulted mixture was extracted with EtOAc. The layers were separated, the organic layer was dried over Na<sub>2</sub>SO<sub>4</sub> and filtered. The solvent was evaporated under reduced pressure. The crude product was purified by reversed-phase chromatography using water-MeCN gradient elution (100:0 to 20 0:100) to give the title compound (290 mg white solid, 50% yield).

<sup>1</sup>H-NMR (400 MHz, DMSO-d<sub>6</sub>) δ ppm: 7.42 (d, 1 H), 7.25-7.15 (m, 3 H), 7.12 (d, 1 H), 6.99 (dd, 1 H), 6.9 (d, 1 H), 4.88 (m, 1 H), 4.45 (s, 2 H), 4.2 (2d, 2 H), 4 (t, 2 H), 3.57 (s, 3 H), 3.4 (t, 2 H), 2.77/2.68 (2dd, 2 H), 2.25 (s, 3 H), 1.8-1.65 (m, 4 H), 1.35 (s, 9 H)

25 **STEP 10 : Preparation of tert-butyl 1-[4-({3-[(5-{1-[(tert-butoxycarbonyl)amino]-3-methoxy-3-oxopropyl}-2-methylphenyl)methyl]-2,2-dioxo-3,4-dihydro-2H-1,2λ<sup>6</sup>,3-benzoxathiazin-6-yl}oxy)butyl]-1H-1,2,3-triazole-4-carboxylate**

To a stirred solution of methyl 3-(3-{{6-(4-azidobutoxy)-2,2-dioxo-2H-1,2λ<sup>6</sup>,3-benzoxathiazin-3(4H)-yl}methyl}-4-methylphenyl)-3-[(tert-butoxycarbonyl)amino]propanoate (1 eq., 225 mg,

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0.372 mmol) in tert-butanol (1.86 mL, 5 mL/mmol) and water (0.75 mL, 2 mL/mmol) tert-butyl prop-2-ynoate (1 eq., 47 mg, 0.372 mmol), copper sulfate (0.06 eq., 3.6 mg, 0.022 mmol) and sodium ascorbate (0.2 eq., 15 mg, 0.075 mmol) were added at RT and the mixture was stirred for 24h. The reaction was quenched with 0.1 M aq. HCl, the resulted mixture was extracted with EtOAc. The layers were separated, the organic layer was dried over Na<sub>2</sub>SO<sub>4</sub> and filtered. The solvent was evaporated under reduced pressure. The crude product was purified by normal phase silica gel chromatography using DCM-EtOAc (100:0 to 80:20) as eluents. The title compound was obtained as a colorless gum (263 mg, 96% yield).

<sup>1</sup>H-NMR (400 MHz, DMSO-d<sub>6</sub>) δ ppm: 8.68 (s, 1 H), 7.45 (d, 1 H), 7.2 (m, 3 H), 7.15 (d, 1 H), 7 (dd, 1 H), 6.9 (d, 1 H), 4.9 (m, 1 H), 4.5 (t, 2 H), 4.45 (s, 2 H), 4.2 (m, 2 H), 3.98 (t, 2 H), 3.55 (s, 3 H), 2.7 (m, 2 H), 2.25 (s, 3 H), 2 (m, 2 H), 1.7 (m, 2 H), 1.5 (s, 9 H), 1.3 (s, 9 H)

**STEP 11 : Preparation of 1-[4-[(3-{[5-(1-amino-3-methoxy-3-oxopropyl)-2-methylphenyl]methyl}-2,2-dioxo-3,4-dihydro-2H-1,2λ<sup>6</sup>,3-benzoxathiazin-6-yl)oxy]butyl]-1H-1,2,3-triazole-4-carboxylic acid hydrochloride**

To a solution of *tert*-butyl 1-[4-[(3-{[5-(1-[(*tert*-butoxycarbonyl)amino]-3-methoxy-3-oxopropyl)-2-methylphenyl]methyl}-2,2-dioxo-3,4-dihydro-2H-1,2λ<sup>6</sup>,3-benzoxathiazin-6-yl)oxy]butyl]-1H-1,2,3-triazole-4-carboxylate (1 eq., 200 mg, 0.274 mmol) in dioxane (10 mL/mmol, 2.74 mL) HCl (4M in dioxane) (5.5 eq., 0.377 mL) was added at 0°C. The reaction mixture was allowed to warm to RT and stirred at RT for 4h. After completion of the reaction the volatiles were evaporated to dryness under reduced pressure. The crude product was used without further purification (174 mg, quant.).

<sup>1</sup>H-NMR (400 MHz, DMSO-d<sub>6</sub>) δ ppm: 8.8-8.4 (m, 3 H), 8.71 (s, 1 H), 7.4 (dd+d, 2 H), 7.3 (d, 1 H), 7.15 (d, 1 H), 7 (dd+d, 2 H), 4.62 (t, 1 H), 4.52 (s, 2 H), 4.5 (t, 2 H), 4.25 (m, 2 H), 4 (t, 2 H), 3.6 (s, 3 H), 3.12/2.98 (2dd, 2 H), 2.3 (s, 3 H), 2.02 (m, 2 H), 1.7 (m, 2 H)

**STEP 12 : Preparation of methyl [4-methyl-10,25,25-trioxo-19,24-dioxa-25λ<sup>6</sup>-thia-1,9,12,13,14-pentaazapentacyclo[18.5.3.1<sup>3,7</sup>.1<sup>11,14</sup>.0<sup>23,27</sup>]triaconta-3(30),4,6,11(29),12,20,22,27-octaen-8-yl]acetate**

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1-{4-[(3-{[5-(1-Amino-3-methoxy-3-oxopropyl)-2-methylphenyl]methyl}-2,2-dioxo-3,4-dihydro-2*H*-1,2λ<sup>6</sup>,3-benzoxathiazin-6-yl)oxy]butyl}-1*H*-1,2,3-triazole-4-carboxylic acid hydrochloride (1 eq., 154 mg, 0.252 mmol) was dissolved in DCM (126 mL, 500 mL/mmol), then TEA (5 eq., 0.176 mL, 1.262 mmol), benzotriazol-1-ol (1.2 eq., 41 mg, 0.303 mmol) and N-(3-dimethylaminopropyl)-N'-ethylcarbodiimide hydrochloride (1.2 eq., 58 mg, 0.303 mmol) were added. The mixture was stirred at RT overnight, quenched with 30 mL water and extracted with DCM. The organic phase was separated, washed with brine, dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated to give the crude product, which was purified by reversed-phase chromatography using water-MeCN gradient elution (64:36 to 28:72) to give the title compound (43 mg white solid, 31% yield).

<sup>1</sup>H-NMR (400 MHz, DMSO-d<sub>6</sub>) δ ppm: 8.2 (d, 1 H), 8.11 (s, 1 H), 7.21 (m, 2 H), 6.98 (d, 1 H), 6.91 (d, 1 H), 6.75 (dd, 1 H), 6 (d, 1 H), 5.61 (m, 1 H), 4.7/4.38 (2m, 2 H), 4.3 (2d, 2 H), 4.18/4.05 (2d, 2 H), 4/3.61 (2m, 2 H), 3.65 (s, 3 H), 3.2/3.1 (2m, 2 H), 2.45 (s, 3 H), 2.4-1.9 (m, 4 H)

### STEP 13 : Preparation of EXAMPLE 72

Using General Procedure 12 starting from methyl [4-methyl-10,25,25-trioxo-19,24-dioxa-25λ<sup>6</sup>-thia-1,9,12,13,14-pentaazapentacyclo[18.5.3.1<sup>3,7</sup>.1<sup>11,14</sup>.0<sup>23,27</sup>]triaconta-3(30),4,6,11(29),12,20,22,27-octaen-8-yl]acetate (1 eq.) as a reactant, the title compound (white solid, quant.) was obtained.

The enantiopure products were obtained by chromatographic separation on chiral column.

#### 25 Example 72a (E1)

HRMS calculated for C<sub>25</sub>H<sub>27</sub>N<sub>5</sub>O<sub>7</sub>S: 541.1631; [M+H]<sup>+</sup> found: 542.1709 (δ=0.9 ppm)

#### Example 72b (E2)

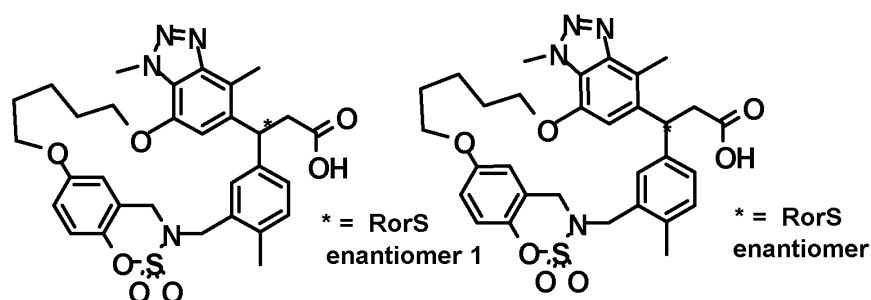
HRMS calculated for C<sub>25</sub>H<sub>27</sub>N<sub>5</sub>O<sub>7</sub>S: 541.1631; [M+H]<sup>+</sup> found: 542.1708 (δ=0.7 ppm)

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<sup>1</sup>H-NMR (400 MHz, DMSO-d<sub>6</sub>) δ ppm: 12.3 (m, 1 H), 9.15 (d, 1 H), 8.66 (s, 1 H), 7.31 (dd, 1 H), 7.25 (d, 1 H), 7.11 (d, 1 H), 7.06 (d, 1 H), 6.86 (dd, 1 H), 6.2 (d, 1 H), 5.41 (m, 1 H), 4.53 (m, 2 H), 4.53/3.99 (dd, 2 H), 4.39/3.77 (dd, 2 H), 3.39/2.81 (2m, 2 H), 2.84/2.72 (2dd, 2 H), 2.35 (s, 3 H), 2.16-1.7 (m, 4 H)

5

**EXAMPLE 73 :** [4,10,14-Trimethyl-29,29-dioxo-17,23,28-trioxa-29λ<sup>6</sup>-thia-1,12,13,14-tetraazahexacyclo[22.5.3.1<sup>3,7</sup>.1<sup>9,16</sup>.0<sup>11,15</sup>.0<sup>27,31</sup>]tetratriaconta-3(34),4,6,9(33),10,12,15,24,26,31-decaen-8-yl]acetic acid



10

**STEP A1 : Preparation of methyl 3-(1,4-dimethyl-1H-benzotriazol-5-yl)-3-[3-(hydroxymethyl)-4-methylphenyl]propanoate**

15 Using General Procedure 6 starting from methyl (2*E*)-3-(1,4-dimethyl-1*H*-benzotriazol-5-yl)prop-2-enoate (1 eq.) and [2-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]methanol (1.3 eq.) as reactants, the title compound (orange oil, 88% yield) was obtained.

20 <sup>1</sup>H-NMR (500 MHz, DMSO-d<sub>6</sub>) δ ppm: 7.57 (d, 1 H), 7.47 (d, 1 H), 7.24 (d, 1 H), 7.1 (dd, 1 H), 7.02 (d, 1 H), 4.99 (t, 1 H), 4.84 (t, 1 H), 4.4 (d, 2 H), 4.23 (s, 3 H), 3.48 (s, 3 H), 3.18/3.13 (dd+dd, 2 H), 2.75 (s, 3 H), 2.15 (s, 3 H)

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**STEP 1 : Preparation of methyl 3-(3-{[6-(benzyloxy)-2,2-dioxo-2*H*-1,2λ<sup>6</sup>,3-benzoxathiazin-3(4*H*)-yl]methyl}-4-methylphenyl)-3-(1,4-dimethyl-1*H*-benzotriazol-5-yl)propanoate**

5 Using General Procedure 7 starting from methyl methyl 3-(1,4-dimethyl-1*H*-benzotriazol-5-yl)-3-[3-(hydroxymethyl)-4-methylphenyl]propanoate (1 eq.) and 6-(benzyloxy)-3,4-dihydro-2*H*-1,2λ<sup>6</sup>,3-benzoxathiazine-2,2-dione (1.2 eq.) as reactants, the title compound (beige solid foam, 84% yield) was obtained.

<sup>1</sup>H-NMR (500 MHz, DMSO-d<sub>6</sub>) δ ppm: 7.56 (d, 1 H), 7.49 (d, 1 H), 7.48-7.32 (m, 5 H), 7.21  
10 (d, 1 H), 7.18 (dd, 1 H), 7.13 (d, 1 H), 7.13 (d, 1 H), 7.07 (dd, 1 H), 6.94 (d, 1 H), 5.1 (s, 2 H), 4.85 (t, 1 H), 4.42 (s, 2 H), 4.22/4.19 (d+d, 2 H), 4.2 (s, 3 H), 3.48 (s, 3 H), 3.22/3.17 (dd+dd, 2 H), 2.75 (s, 3 H), 2.22 (s, 3 H)

**STEP 2 : Preparation of methyl 3-(3-{[6-(benzyloxy)-2,2-dioxo-2*H*-1,2λ<sup>6</sup>,3-benzoxathiazin-3(4*H*)-yl]methyl}-4-methylphenyl)-3-(7-bromo-1,4-dimethyl-1*H*-benzotriazol-5-yl)propanoate**

15

Methyl 3-(3-{[6-(benzyloxy)-2,2-dioxo-2*H*-1,2λ<sup>6</sup>,3-benzoxathiazin-3(4*H*)-yl]methyl}-4-methylphenyl)-3-(1,4-dimethyl-1*H*-benzotriazol-5-yl)propanoate (1 eq., 1 g, 1.59 mmol) was  
20 dissolved in nitromethane (20 mL), then Oxone ® (3 eq., 2.31 g, 4.79 mmol) and potassium bromide (1.2 eq., 0.23 g, 1.92 mmol) were added. The reaction mixture was stirred overnight at 60°C, diluted with DCM (30 mL) and washed with water (50 mL). The organic phase was dried over MgSO<sub>4</sub>, filtered and concentrated under reduced pressure to give the crude product, which was purified by preparative reversed-phase chromatography using 5 mM aq. NH<sub>4</sub>HCO<sub>3</sub>-MeCN  
25 gradient elution (95:5 to 0:100) to give the title compound (35% yield).

<sup>1</sup>H-NMR (500 MHz, DMSO-d<sub>6</sub>) δ ppm: 7.68 (s, 1 H), 7.49-7.31 (m, 5 H), 7.25 (d, 1 H), 7.21 (dd, 1 H), 7.16 (d, 1 H), 7.13 (d, 1 H), 7.06 (dd, 1 H), 6.96 (d, 1 H), 5.1 (s, 2 H), 4.83 (t, 1 H), 4.47/4.42 (d+d, 2 H), 4.41 (s, 3 H), 4.22 (s, 2 H), 3.49 (s, 3 H), 3.24 (d, 2 H), 2.73 (s, 3 H), 2.23 (s, 3 H)



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**STEP 3 : Preparation of methyl 3-(3-{[6-(benzyloxy)-2,2-dioxo-2*H*-1,2λ<sup>6</sup>,3-benzoxathiazin-3(4*H*)-yl]methyl}-4-methylphenyl)-3-(7-{[5-(benzyloxy)pentyl]oxy}-1,4-dimethyl-1*H*-benzotriazol-5-yl)propanoate**

5 Methyl 3-(3-{[6-(benzyloxy)-2,2-dioxo-2*H*-1,2λ<sup>6</sup>,3-benzoxathiazin-3(4*H*)-yl]methyl}-4-methylphenyl)-3-(7-bromo-1,4-dimethyl-1*H*-benzotriazol-5-yl)propanoate (1 eq., 391 mg, 0.554 mmol) was dissolved in toluene (20 mL), then 5-benzyloxypentan-1-ol (10 eq., 1.07 g, 5.54 mmol), Cs<sub>2</sub>CO<sub>3</sub> (10 eq., 1.81 g, 5.54 mmol), 2-(di-*tert*-butylphosphino)-1,1'-binaphtyl (0.1 eq., 22 mg, 0.055 mmol) and palladium diacetate catalyst (0.08 eq., 10 mg, 0.044 mmol) were  
10 added. The reaction mixture was stirred for 3 days at 70°C under inert atmosphere. The solvent was evaporated, then the mixture was diluted with EtOAc (20 mL) and water (20 mL). The organic phase was separated, the aq. phase was extracted with further 3x20 mL EtOAc. The combined organic phase was dried over MgSO<sub>4</sub>, filtered, concentrated under reduced pressure to give the crude product, which was purified by preparative reversed-phase chromatography  
15 using 5 mM aq. NH<sub>4</sub>HCO<sub>3</sub>-MeCN gradient elution (95:5 to 0:100) to give the title compound (colorless oil, 11% yield).

<sup>1</sup>H-NMR (500 MHz, DMSO-d<sub>6</sub>) δ ppm: 7.47-7.19 (m, 12 H), 7.13 (d, 1 H), 7.13 (d, 1 H), 7.06 (dd, 1 H), 6.93 (d, 1 H), 6.88 (s, 1 H), 5.08 (s, 2 H), 4.8 (t, 1 H), 4.47/4.42 (d+d, 2 H), 4.42 (s, 2 H), 4.29 (s, 3 H), 4.24/4.19 (d+d, 2 H), 4.15/4.06 (m+m, 2 H), 3.49 (s, 3 H), 3.43 (t, 2 H), 3.22  
20 (m, 2 H), 2.62 (s, 3 H), 2.21 (s, 3 H), 1.84-1.03 (m, 6 H)

**STEP 4 : Preparation of methyl 3-{3-[(6-hydroxy-2,2-dioxo-2*H*-1,2λ<sup>6</sup>,3-benzoxathiazin-3(4*H*)-yl)methyl]-4-methylphenyl}-3-{7-[(5-hydroxypentyl)oxy]-1,4-dimethyl-1*H*-benzotriazol-5-yl}propanoate**

25

Using General Procedure 8 starting from methyl 3-(3-{[6-(benzyloxy)-2,2-dioxo-2*H*-1,2λ<sup>6</sup>,3-benzoxathiazin-3(4*H*)-yl]methyl}-4-methylphenyl)-3-(7-{[5-(benzyloxy)pentyl]oxy}-1,4-dimethyl-1*H*-benzotriazol-5-yl)propanoate (1 eq.) as a reactant, the title compound (white solid foam, 82% yield) was obtained.

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<sup>1</sup>H-NMR (500 MHz, DMSO-d<sub>6</sub>) δ ppm: 9.69 (s, 1 H), 7.24 (d, 1 H), 7.21 (dd, 1 H), 7.13 (d, 1 H), 6.99 (d, 1 H), 6.88 (s, 1 H), 6.78 (dd, 1 H), 6.58 (d, 1 H), 4.79 (t, 1 H), 4.42/4.36 (d+d, 2 H), 4.39 (brs, 1 H), 4.35 (s, 3 H), 4.23/4.16 (d+d, 2 H), 4.16/4.07 (m+m, 2 H), 3.51 (s, 3 H), 3.42 (m, 2 H), 3.23/3.19 (m+m, 2 H), 2.61 (s, 3 H), 2.22 (s, 3 H), 1.85-1.43 (m, 6 H)

5

**STEP 5 : Preparation of methyl 3-{7-[(5-chloropentyl)oxy]-1,4-dimethyl-1*H*-benzotriazol-5-yl}-3-{3-[(6-hydroxy-2,2-dioxo-2*H*-1,2λ<sup>6</sup>,3-benzoxathiazin-3(4*H*)-yl)methyl]-4-methylphenyl}propanoate hydrochloride**

10 Using General Procedure 10 starting from methyl 3-{3-[(6-hydroxy-2,2-dioxo-2*H*-1,2λ<sup>6</sup>,3-benzoxathiazin-3(4*H*)-yl)methyl]-4-methylphenyl}-3-{7-[(5-hydroxypentyl)oxy]-1,4-dimethyl-1*H*-benzotriazol-5-yl}propanoate (1 eq.) as a reactant, the title compound (off-white solid foam, quant.) was obtained.

15 <sup>1</sup>H-NMR (500 MHz, DMSO-d<sub>6</sub>) δ ppm: 9.71 (brs, 1 H), 7.24 (d, 1 H), 7.21 (dd, 1 H), 7.13 (d, 1 H), 6.99 (d, 1 H), 6.89 (s, 1 H), 6.79 (dd, 1 H), 6.58 (d, 1 H), 4.79 (t, 1 H), 4.42/4.37 (d+d, 2 H), 4.35 (s, 3 H), 4.23/4.17 (d+d, 2 H), 4.17/4.07 (m+m, 2 H), 3.66 (t, 2 H), 3.51 (s, 3 H), 3.24/3.19 (dd+dd, 2 H), 2.61 (s, 3 H), 2.22 (s, 3 H), 1.81 (m, 2 H), 1.79 (m, 2 H), 1.59 (m, 2 H)

20 **STEP 6 : Preparation of methyl [4,10,14-trimethyl-29,29-dioxo-17,23,28-trioxa-29λ<sup>6</sup>-thia-1,12,13,14-tetraazahexacyclo[22.5.3.1<sup>3,7</sup>.1<sup>9,16</sup>.0<sup>11,15</sup>.0<sup>27,31</sup>]tetratriaconta-3(34),4,6,9(33),10,12,15,24,26,31-decaen-8-yl]acetate**

25 Using General Procedure 11 starting from methyl 3-{7-[(5-chloropentyl)oxy]-1,4-dimethyl-1*H*-benzotriazol-5-yl}-3-{3-[(6-hydroxy-2,2-dioxo-2*H*-1,2λ<sup>6</sup>,3-benzoxathiazin-3(4*H*)-yl)methyl]-4-methylphenyl}propanoate hydrochloride (1 eq.) as a reactant, the title compound (beige solid, 19%) was obtained.

30 <sup>1</sup>H-NMR (500 MHz, DMSO-d<sub>6</sub>) δ ppm: 7.4 (dd, 1 H), 7.2 (d, 1 H), 7.1 (s, 1 H), 7.07 (m, 1 H), 7.07 (d, 1 H), 6.97 (m, 1 H), 6.96 (m, 1 H), 4.77 (t, 1 H), 4.42/4.26 (d+d, 2 H), 4.35 (s, 3 H), 4.29/4.07 (m+m, 2 H), 4.18 (t, 2 H), 4.11/4.05 (d+d, 2 H), 3.49 (s, 3 H), 3.32/3.18 (dd+dd, 2 H), 2.52 (s, 3 H), 2.31 (s, 3 H), 2.1-1.58 (m, 6 H)

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**STEP 7 : Preparation of EXAMPLE 73**

Using General Procedure 12 starting from methyl [4,10,14-trimethyl-29,29-dioxo-17,23,28-trioxa-29 $\lambda^6$ -thia-1,12,13,14-tetraazahexacyclo[22.5.3.1<sup>3,7</sup>.1<sup>9,16</sup>.0<sup>11,15</sup>.0<sup>27,31</sup>]tetratriaconta-3(34),4,6,9(33),10,12,15,24,26,31-decaen-8-yl]acetate (1 eq.) as a reactant, the title compound (white solid, 72% yield) was obtained.

The enantiopure products were obtained by chromatographic separation on chiral column.

**Example 73a (E1)**

**HRMS** calculated for C<sub>31</sub>H<sub>34</sub>N<sub>4</sub>O<sub>7</sub>S: 606.2148; [M+H]<sup>+</sup> found: 607.2223 ( $\delta$  = 0.3 ppm)

**Example 73b (E2)**

**HRMS** calculated for C<sub>31</sub>H<sub>34</sub>N<sub>4</sub>O<sub>7</sub>S: 606.2148; [M+H]<sup>+</sup> found: 607.2223 ( $\delta$  = 0.3 ppm)

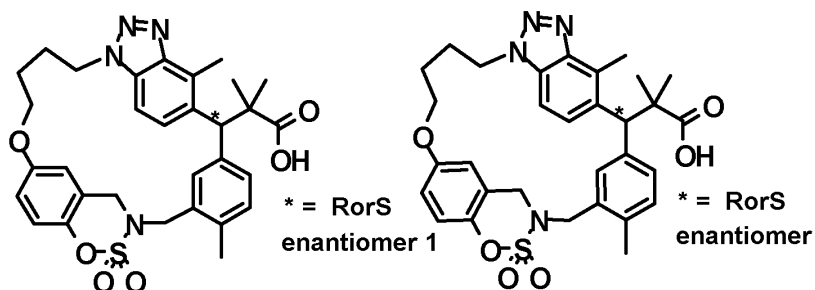
**<sup>1</sup>H-NMR** (500 MHz, DMSO-d<sub>6</sub>)  $\delta$  ppm 7.4 (d, 1 H), 7.19 (d, 1 H), 7.13 (s, 1 H), 7.06 (d, 1 H), 7.02 (d, 1 H), 6.99 (d, 1 H), 6.96 (dd, 1 H), 4.73 (t, 1 H), 4.41/4.29 (d+d, 2 H), 4.35 (s, 3 H), 4.28/4.08 (m+m, 2 H), 4.17 (t, 2 H), 4.14/3.99 (d+d, 2 H), 3.16/3.02 (dd+dd, 2 H), 2.5 (s, 3 H), 2.31 (s, 3 H), 2/1.92 (m+m, 2 H), 1.9/1.74 (m+m, 2 H), 1.73/1.63 (m+m, 2 H)

**<sup>13</sup>C-NMR** (125 MHz, DMSO-d<sub>6</sub>)  $\delta$  ppm: 173.5, 155.7, 148.3, 144.8, 143.6, 142.3, 137.6, 136.4, 132.8, 131.2, 129.9, 129.8, 123.9, 119.4, 118.1, 117.9, 117.6, 113.8, 107, 68.3, 68.1, 51.9, 49.8, 42.2, 41.7, 36.9, 27.4, 26.7, 21.1, 18.7, 12.8

**EXAMPLE 74 : 2-[4,31-Dimethyl-27,27-dioxo-21,26-dioxa-27 $\lambda^6$ -thia-1,14,15,16-**

**tetraazahexacyclo[20.5.3.1<sup>3,7</sup>.1<sup>9,13</sup>.0<sup>12,16</sup>.0<sup>25,29</sup>]dotriaconta-3(32),4,6,9(31),10,12,14,22,24,29-decaen-8-yl]-2-methylpropanoic acid**

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### STEP 1 : Preparation of 2-[(5-bromo-2-methylphenyl)methoxy]oxane

- 5 To a solution of (5-bromo-2-methylphenyl)methanol (1 eq., 7.05 g, 35.1 mmol) in DCM (50 mL) at 0°C 4-methylbenzene-1-sulfonic acid monohydrate (0.01 equiv., 0.07 g, 0.351 mmol) was added followed by addition of 3,4-dihydro-2H-pyran (1.1 equiv., 3.52 mL, 38.6 mmol). The reaction mixture was warmed to RT and stirred for 1h before quenching with saturated NaHCO<sub>3</sub> (30 mL). The phases were separated. The aq. phase was extracted with DCM (30
- 10 mL), the combined organic phases were dried over MgSO<sub>4</sub> and filtered. The solvent was removed under reduced pressure to give the title compound (10 g, quant.).
- <sup>1</sup>H-NMR (500 MHz, DMSO-d<sub>6</sub>) δ ppm: 7.49 (d, 1 H), 7.38 (dd, 1 H), 7.15 (d, 1 H), 4.7 (t, 1 H), 4.66/4.42 (d+d, 2 H), 3.77/3.49 (m+m, 2 H), 2.22 (s, 3 H), 1.82-1.41 (m, 6 H)

### 15 STEP 2 : Preparation of 4-methyl-3-[[[(oxan-2-yl)oxy]methyl]benzaldehyde

- To a stirred solution of 2-[(5-bromo-2-methylphenyl)methoxy]oxane (1 eq., 5 g, 18 mmol) in THF (40 mL) *N*<sup>1</sup>,*N*<sup>1</sup>,*N*<sup>2</sup>,*N*<sup>2</sup>-tetramethylethane-1,2-diamine (1.5 eq., 3.1 g, 26 mmol) was added. The mixture was cooled to -75 °C, butyllithium (1.5 eq., 26 mmol) was added dropwise and the
- 20 mixture was stirred at -75 °C for further 30 min. DMF (2 eq., 2.6 g, 35 mmol) was added dropwise, the temperature was allowed to warm to RT and the mixture was stirred for further 1h at Rt. After completion of the reaction the mixture was poured into 80 ml of water and extracted with EtOAc. The separated organic layer was dried over MgSO<sub>4</sub>, filtered and

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evaporated to dryness. The crude oil was purified by normal phase silica gel chromatography using heptane-EtOAc (100:0 to 0:100) as an eluent to give the title compound (4 g, 97% yield).

<sup>1</sup>H-NMR (500 MHz, DMSO-d<sub>6</sub>) δ ppm: 9.97 (s, 1 H), 7.87 (d, 1 H), 7.75 (dd, 1 H), 7.42 (d, 1 H), 4.76/4.51 (d+d, 2 H), 4.73 (dd, 1 H), 3.79/3.5 (m+m, 2 H), 2.36 (s, 3 H), 1.83-1.41 (m, 6 H)

**STEP 3 : Preparation of {1-[4-(benzyloxy)butyl]-4-methyl-1H-benzotriazol-5-yl}(4-methyl-3-[[oxan-2-yl]oxy]methyl}phenyl)methanol**

10 1-[4-(Benzyloxy)butyl]-5-bromo-4-methyl-1H-benzotriazole (1 eq., 1.04 g, 2.78 mmol) was dissolved in THF (40 mL) and *N*<sup>1</sup>,*N*<sup>1</sup>,*N*<sup>2</sup>,*N*<sup>2</sup>-tetramethylethane-1,2-diamine (1.5 eq., 484 mg, 4.17 mmol) was added to it. The mixture was cooled to -75 °C, butyllithium (3 eq., 8.34 mmol) was added dropwise and the mixture was stirred at -75 °C for 30 min. 4-methyl-3-[[oxan-2-yl]oxy]methyl}benzaldehyde (2 eq., 1.3 g, 5.5 mmol) dissolved in THF (10 mL) was added and  
15 the reaction mixture was stirred at RT for 2h. After completion of the reaction the mixture was poured into 100 ml of water, extracted with 2x50 ml of EtOAc, the combined organic layer was dried over MgSO<sub>4</sub>, filtered, evaporated under reduced pressure to dryness. The crude oil was purified by normal phase silica gel chromatography using heptane-EtOAc (100:0 to 0:100) as an eluent to give the title compound (0.4 g, 27% yield).

20 <sup>1</sup>H-NMR (500 MHz, DMSO-d<sub>6</sub>) δ ppm: 7.61 (d, 1 H), 7.59 (d, 1 H), 7.35-7.23 (m, 5 H), 7.25 (d, 1 H), 7.17 (dd, 1 H), 7.09 (d, 1 H), 6.05 (d, 1 H), 5.89 (d, 1 H), 4.67 (t, 2 H), 4.61/4.37 (d+d, 2 H), 4.59 (dd, 1 H), 4.4 (s, 2 H), 3.67/3.37 (m+m, 2 H), 3.42 (t, 2 H), 2.67/2.66 (s, 3 H), 2.21 (s, 3 H), 1.94 (m, 2 H), 1.7-1.3 (m, 6 H), 1.49 (m, 2 H)

25 **STEP 4 : Preparation of methyl 3-{1-[4-(benzyloxy)butyl]-4-methyl-1H-benzotriazol-5-yl}-2,2-dimethyl-3-(4-methyl-3-[[oxan-2-yl]oxy]methyl}phenyl)propanoate**

{1-[4-(Benzyloxy)butyl]-4-methyl-1H-benzotriazol-5-yl}(4-methyl-3-[[oxan-2-yl]oxy]methyl} phenyl)methanol (1 eq., 4.04 g, 7.62 mmol) was dissolved in MeCN (50 mL)  
30 and 2,2,2-trichloroacetonitrile (2 eq., 2.2 g, 15.25 mmol) and 2,3,4,6,7,8,9,10-

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octahydropyrimido[1,2-*a*]azepine (0.05 eq., 58.06 mg, 0.38 mmol) were added. The mixture was stirred at RT for 45 min, then [(1-methoxy-2-methylprop-1-en-1-yl)oxy](trimethyl)silane (2.5 eq., 3.32 g, 19.07 mmol) and 1,1,1-trifluoro-*N*-(trifluoromethanesulfonyl)-methanesulfonamide (0.1 eq., 0.21 g, 0.76 mmol) were added. The reaction mixture was stirred at RT for 2h. After completion of the reaction 40 ml of sat. aq. NaHCO<sub>3</sub> was added and the layers were separated. The aq. layer was extracted with 2x50 mL of EtOAc, the combined organic layer was dried over MgSO<sub>4</sub>, filtered and evaporated under reduced pressure to give the title compound (4.6 g, 98% yield).

<sup>1</sup>H-NMR (500 MHz, DMSO-d<sub>6</sub>) δ ppm: 7.61-7.54 (d, 1 H), 7.61-7.54 (d, 1 H), 7.35-7.23 (m, 5 H), 7.22 (d, 1 H), 7.13 (dd, 1 H), 7.06 (d, 1 H), 4.77 (s, 1 H), 4.66 (t, 2 H), 4.58/4.38 (d+d, 2 H), 4.57 (m, 1 H), 4.4 (s, 2 H), 3.67/3.35 (m+m, 2 H), 3.43 (s, 3 H), 3.42 (t, 2 H), 2.7/2.69 (s, 3 H), 2.19 (s, 3 H), 1.94 (m, 2 H), 1.75-1.31 (m, 6 H), 1.52 (m, 2 H), 1.3 (s, 3 H), 1.23 (s, 3 H)

**STEP 5 : Preparation of methyl 3-{1-[4-(benzyloxy)butyl]-4-methyl-1*H*-benzotriazol-5-yl}-3-[3-(hydroxymethyl)-4-methylphenyl]-2,2-dimethylpropanoate**

Methyl 3-{1-[4-(benzyloxy)butyl]-4-methyl-1*H*-benzotriazol-5-yl}-2,2-dimethyl-3-(4-methyl-3-[[[(oxan-2-yl)oxy]methyl]phenyl]propanoate (1 eq., 4.6 g, 7.49 mmol) was dissolved in MeOH (80 mL) and 4-methylbenzenesulfonic acid pyridine complex (0.05 eq., 94.2 mg, 0.375 mmol) was added. After stirring at 55 °C for 2h the reaction mixture was cooled to RT, evaporated to dryness under reduced pressure, dissolved in DCM, extracted with 2x50 mL of sat. aq. NaHCO<sub>3</sub>, then with 50 ml of brine. The organic layer was dried over MgSO<sub>4</sub>, filtered and evaporated under reduced pressure to give the title compound (3.93 g, 99% yield).

<sup>1</sup>H-NMR (500 MHz, DMSO-d<sub>6</sub>) δ ppm: 7.61 (d, 1 H), 7.59 (d, 1 H), 7.36-7.23 (m, 5 H), 7.28 (d, 1 H), 7.09 (dd, 1 H), 7.01 (d, 1 H), 5.01 (t, 1 H), 4.76 (s, 1 H), 4.66 (t, 2 H), 4.41 (d, 2 H), 4.4 (s, 2 H), 3.43 (t, 2 H), 3.42 (s, 3 H), 2.7 (s, 3 H), 2.15 (s, 3 H), 1.95 (m, 2 H), 1.52 (m, 2 H), 1.3 (s, 3 H), 1.24 (s, 3 H)

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**STEP 6: Preparation of methyl 3-{1-[4-(benzyloxy)butyl]-4-methyl-1*H*-benzotriazol-5-yl}-3-(3-{[6-(benzyloxy)-2,2-dioxo-2*H*-1,2λ<sup>6</sup>,3-benzoxathiazin-3(4*H*)-yl]methyl}-4-methylphenyl)-2,2-dimethylpropanoate**

5 Using General Procedure 7 starting from methyl 3-{1-[4-(benzyloxy)butyl]-4-methyl-1*H*-benzotriazol-5-yl}-3-(3-(hydroxymethyl)-4-methylphenyl)-2,2-dimethylpropanoate (1 eq.) and 6-(benzyloxy)-3,4-dihydro-2*H*-1,2λ<sup>6</sup>,3-benzoxathiazine-2,2-dione (1 eq.) as reactants, the title compound (62% yield) was obtained.

10 <sup>1</sup>H-NMR (500 MHz, DMSO-d<sub>6</sub>) δ ppm: 7.59 (d, 1 H), 7.57 (d, 1 H), 7.46 (dm, 2 H), 7.41 (tm, 2 H), 7.34 (tm, 1 H), 7.3 (tm, 2 H), 7.25 (tm, 1 H), 7.25 (dm, 2 H), 7.23 (d, 1 H), 7.19 (dd, 1 H), 7.14 (d, 1 H), 7.12 (d, 1 H), 7.08 (dd, 1 H), 6.89 (d, 1 H), 5.1 (s, 2 H), 4.77 (s, 1 H), 4.63 (t, 2 H), 4.42 (s, 2 H), 4.38 (s, 2 H), 4.28/4.17 (d+d, 2 H), 3.44 (s, 3 H), 3.4 (t, 2 H), 2.71 (s, 3 H), 2.22 (s, 3 H), 1.93 (m, 2 H), 1.49 (m, 2 H), 1.29/1.25 (s+s, 6 H)

15 **STEP 7 : Preparation of methyl 3-[1-(4-hydroxybutyl)-4-methyl-1*H*-benzotriazol-5-yl]-3-{3-[(6-hydroxy-2,2-dioxo-2*H*-1,2λ<sup>6</sup>,3-benzoxathiazin-3(4*H*)-yl)methyl]-4-methylphenyl}-2,2-dimethylpropanoate**

20 Using General Procedure 8 starting from methyl 3-{1-[4-(benzyloxy)butyl]-4-methyl-1*H*-benzotriazol-5-yl}-3-(3-{[6-(benzyloxy)-2,2-dioxo-2*H*-1,2λ<sup>6</sup>,3-benzoxathiazin-3(4*H*)-yl]methyl}-4-methylphenyl)-2,2-dimethylpropanoate (1 eq.) as a reactant, the title compound (99% yield) was obtained.

25 <sup>1</sup>H-NMR (500 MHz, DMSO-d<sub>6</sub>) δ ppm: 9.71 (s, 1 H), 7.61 (m, 1 H), 7.61 (m, 1 H), 7.21 (d, 1 H), 7.19 (dd, 1 H), 7.13 (d, 1 H), 7 (d, 1 H), 6.8 (dd, 1 H), 6.57 (d, 1 H), 4.76 (s, 1 H), 4.65 (t, 2 H), 4.44 (brs, 1 H), 4.37 (s, 2 H), 4.26/4.15 (d+d, 2 H), 3.45 (s, 3 H), 3.39 (t, 2 H), 2.71 (s, 3 H), 2.23 (s, 3 H), 1.91 (qn, 2 H), 1.38 (qn, 2 H), 1.3 (s, 3 H), 1.25 (s, 3 H)

30 **STEP 8 : Preparation of methyl 3-[1-(4-chlorobutyl)-4-methyl-1*H*-benzotriazol-5-yl]-3-{3-[(6-hydroxy-2,2-dioxo-2*H*-1,2λ<sup>6</sup>,3-benzoxathiazin-3(4*H*)-yl)methyl]-4-methylphenyl}-2,2-dimethylpropanoate**

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Using General Procedure 10 starting from methyl 3-[1-(4-hydroxybutyl)-4-methyl-1*H*-benzotriazol-5-yl]-3-{3-[(6-hydroxy-2,2-dioxo-2*H*-1,2λ<sup>6</sup>,3-benzoxathiazin-3(4*H*)-yl)methyl]-4-methylphenyl}-2,2-dimethylpropanoate (1 eq.) as a reactant, the title compound (98% yield) was obtained.

<sup>1</sup>H-NMR (500 MHz, DMSO-d<sub>6</sub>) δ ppm: 9.6 (brs, 1 H), 7.65 (d, 1 H), 7.62 (d, 1 H), 7.21 (d, 1 H), 7.2 (dd, 1 H), 7.13 (d, 1 H), 7.01 (d, 1 H), 6.81 (dd, 1 H), 6.58 (d, 1 H), 4.77 (s, 1 H), 4.7 (t, 2 H), 4.37 (s, 2 H), 4.27/4.15 (d+d, 2 H), 3.65 (t, 2 H), 3.45 (s, 3 H), 2.71 (s, 3 H), 2.23 (s, 3 H), 2.01 (qn, 2 H), 1.71 (qn, 2 H), 1.3 (s, 3 H), 1.26 (s, 3 H)

**STEP 9 : Preparation of methyl 2-[4,31-dimethyl-27,27-dioxo-21,26-dioxa-27λ<sup>6</sup>-thia-1,14,15,16-tetraazahexacyclo[20.5.3.1<sup>3,7</sup>.1<sup>9,13</sup>.0<sup>12,16</sup>.0<sup>25,29</sup>]dotriaconta-3(32),4,6,9(31),10,12,14,22,24,29-decaen-8-yl]-2-methylpropanoate**

Using General Procedure 11 starting from methyl 3-[1-(4-chlorobutyl)-4-methyl-1*H*-benzotriazol-5-yl]-3-{3-[(6-hydroxy-2,2-dioxo-2*H*-1,2λ<sup>6</sup>,3-benzoxathiazin-3(4*H*)-yl)methyl]-4-methylphenyl}-2,2-dimethylpropanoate (1 eq., 3.2 g, 4.99 mmol) as a reactant, the title compound (2.95 g, 97% yield) was obtained.

<sup>1</sup>H-NMR (500 MHz, DMSO-d<sub>6</sub>) δ ppm: 7.6 (d, 1 H), 7.5 (d, 1 H), 7.38 (dd, 1 H), 7.27 (d, 1 H), 7.01 (d, 1 H), 6.81 (dd, 1 H), 6.67 (d, 1 H), 5.85 (br., 1 H), 4.81 (s, 1 H), 4.8/4.73 (m+m, 2 H), 4.35/3.84 (brd+brd, 2 H), 4.08/3.65 (d+d, 2 H), 3.7/3.43 (br+m, 2 H), 3.43 (s, 3 H), 2.63 (s, 3 H), 2.33 (s, 3 H), 2.21/2.06 (m+m, 2 H), 1.84/1.64 (m+m, 2 H), 1.27/1.13 (s+s, 6 H)

**STEP 10 : Preparation of EXAMPLE 74**

Using General Procedure 12 starting from methyl 2-[4,31-dimethyl-27,27-dioxo-21,26-dioxa-27λ<sup>6</sup>-thia-1,14,15,16-tetraazahexacyclo[20.5.3.1<sup>3,7</sup>.1<sup>9,13</sup>.0<sup>12,16</sup>.0<sup>25,29</sup>]dotriaconta-3(32),4,6,9(31),10,12,14,22,24,29-decaen-8-yl]-2-methylpropanoate as a reactant, the title compound was obtained.

The enantiopure products were obtained by chromatographic separation on chiral column.



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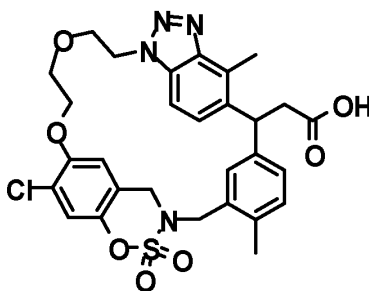
**Example 74a (E1)**HRMS calculated for C<sub>31</sub>H<sub>34</sub>N<sub>4</sub>O<sub>6</sub>S: 590.2199; [M+H]<sup>+</sup> found: 591.2272 (δ = 0.0 ppm)5 **Example 74b (E2)**HRMS calculated for C<sub>31</sub>H<sub>34</sub>N<sub>4</sub>O<sub>6</sub>S: 590.2199; [M+H]<sup>+</sup> found: 591.2277 (δ = 0.9 ppm)

**<sup>1</sup>H-NMR** (500 MHz, DMSO-d<sub>6</sub>) δ ppm: 12.34 (brs, 1 H), 7.61 (d, 1 H), 7.53 (d, 1 H), 7.46 (dd, 1 H), 7.26 (d, 1 H), 7 (d, 1 H), 6.81 (dd, 1 H), 6.61 (brs, 1 H), 5.85 (brs, 1 H), 4.84 (s, 1 H), 4.79/4.73 (m+m, 2 H), 4.27/3.87 (brd+brd, 2 H), 4.06/3.71 (brd+brd, 2 H), 3.71/3.43 (m+m, 2 H), 2.62 (s, 3 H), 2.33 (s, 3 H), 2.22/2.08 (m+m, 2 H), 1.83/1.64 (m+m, 2 H), 1.25 (s, 3 H), 1.07 (s, 3 H)

**<sup>13</sup>C-NMR** (125 MHz, DMSO-d<sub>6</sub>) δ ppm: 133.3, 130.9, 130.6, 128.3, 119.6, 117.6, 111.1, 107.2, 67.9, 52, 51.6, 48.7, 48.2, 26.6, 25.6, 25.3, 24.7, 18.5, 14.2

15

**EXAMPLE 75:** [24-Chloro-4,32-dimethyl-28,28-dioxo-19,22,27-trioxa-28λ<sup>6</sup>-thia-1,14,15,16-tetraazahexacyclo[21.5.3.1<sup>3,7</sup>.1<sup>9,13</sup>.0<sup>12,16</sup>.0<sup>26,30</sup>]tritiaconta-3(33),4,6,9(32),10,12,14,23,25,30-decaen-8-yl]acetic acid



20

**STEP 1:** Preparation of ethyl 3-(1-{2-[2-(benzyloxy)ethoxy]ethyl}-4-methyl-1H-benzotriazol-5-yl)-3-[3-(hydroxymethyl)-4-methylphenyl]propanoate

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Using General Procedure 6 starting from ethyl (2*E*)-3-(1-{2-[2-(benzyloxy)ethoxy]ethyl}-4-methyl-1*H*-benzotriazol-5-yl)prop-2-enoate (1 eq.) and [2-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]methanol (1.3 eq.) as reactants, the title compound (yellow oil, 71% yield) was obtained.

5 <sup>1</sup>H-NMR (500 MHz, DMSO-d<sub>6</sub>) δ ppm: 7.61 (d, 1 H), 7.4 (d, 1 H), 7.33-7.17 (m, 5 H), 7.26 (d, 1 H), 7.08 (dd, 1 H), 7.01 (d, 1 H), 4.99 (t, 1 H), 4.82 (t, 1 H), 4.81 (t, 2 H), 4.39 (d, 2 H), 4.32 (s, 2 H), 3.92 (q, 2 H), 3.89 (t, 2 H), 3.52 (m, 2 H), 3.43 (m, 2 H), 3.12/3.07 (dd+dd, 2 H), 2.75 (s, 3 H), 2.14 (s, 3 H), 1.01 (t, 3 H)

10 **STEP 2: Preparation of ethyl 3-(3-{[6-(benzyloxy)-7-chloro-2,2-dioxo-2*H*-1,2λ<sup>6</sup>,3-benzoxathiazin-3(4*H*)-yl]methyl}-4-methylphenyl)-3-(1-{2-[2-(benzyloxy)ethoxy]ethyl}-4-methyl-1*H*-benzotriazol-5-yl)propanoate**

Using General Procedure 7 starting from ethyl 3-(1-{2-[2-(benzyloxy)ethoxy]ethyl}-4-methyl-1*H*-benzotriazol-5-yl)-3-[3-(hydroxymethyl)-4-methylphenyl]propanoate (1 eq.) and 6-(benzyloxy)-7-chloro-3,4-dihydro-2*H*-1,2λ<sup>6</sup>,3-benzoxathiazine-2,2-dione (0.83 eq.) as reactants, the title compound (off-white solid, 95% yield) was obtained.

15 <sup>1</sup>H-NMR (500 MHz, DMSO-d<sub>6</sub>) δ ppm: 7.6 (d, 1 H), 7.51-7.13 (m, 10 H), 7.46 (s, 1 H), 7.43 (d, 1 H), 7.26 (s, 1 H), 7.25 (d, 1 H), 7.17 (dd, 1 H), 7.11 (d, 1 H), 5.16 (s, 2 H), 4.84 (t, 1 H), 4.8 (t, 2 H), 4.48/4.44 (d+d, 2 H), 4.28 (s, 2 H), 4.24/4.19 (d+d, 2 H), 3.91 (q, 2 H), 3.87 (t, 2 H), 3.5 (m, 2 H), 3.4 (m, 2 H), 3.18/3.12 (dd+dd, 2 H), 2.76 (s, 3 H), 2.19 (s, 3 H), 0.97 (t, 3 H)

25 **STEP 3: Preparation of ethyl 3-{3-[(7-chloro-6-hydroxy-2,2-dioxo-2*H*-1,2λ<sup>6</sup>,3-benzoxathiazin-3(4*H*)-yl)methyl]-4-methylphenyl}-3-{1-[2-(2-hydroxyethoxy)ethyl]-4-methyl-1*H*-benzotriazol-5-yl}propanoate**

Using General Procedure 8 starting from ethyl 3-(3-{[6-(benzyloxy)-7-chloro-2,2-dioxo-2*H*-1,2λ<sup>6</sup>,3-benzoxathiazin-3(4*H*)-yl]methyl}-4-methylphenyl)-3-(1-{2-[2-(benzyloxy)ethoxy]ethyl}-4-methyl-1*H*-benzotriazol-5-yl)propanoate (1 eq.) as a reactant, the title compound (white solid foam, quant.) was obtained.

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<sup>1</sup>H-NMR (500 MHz, DMSO-d<sub>6</sub>) δ ppm: 10.48 (s, 1 H), 7.62 (d, 1 H), 7.5 (d, 1 H), 7.31 (s, 1 H), 7.28 (d, 1 H), 7.18 (dd, 1 H), 7.13 (d, 1 H), 6.85 (s, 1 H), 4.83 (t, 1 H), 4.8 (t, 2 H), 4.54 (m, 1 H), 4.46/4.41 (d+d, 2 H), 4.25/4.2 (d+d, 2 H), 3.93 (q, 2 H), 3.88 (t, 2 H), 3.37 (m, 2 H), 3.37 (m, 2 H), 3.17 (d, 2 H), 2.76 (s, 3 H), 2.22 (s, 3 H), 1 (t, 3 H)

5

**STEP 4 : Preparation of ethyl [24-chloro-4,32-dimethyl-28,28-dioxo-19,22,27-trioxa-28λ<sup>6</sup>-thia-1,14,15,16-tetraazahexacyclo[21.5.3.1<sup>3,7</sup>.1<sup>9,13</sup>.0<sup>12,16</sup>.0<sup>26,30</sup>]tritiaconta-3(33),4,6,9(32),10,12,14,23,25,30-decaen-8-yl]acetate**

10 Ethyl 3-{3-[(7-chloro-6-hydroxy-2,2-dioxo-2*H*-1,2λ<sup>6</sup>,3-benzoxathiazin-3(4*H*)-yl)methyl]-4-methylphenyl}-3-{1-[2-(2-hydroxyethoxy)ethyl]-4-methyl-1*H*-benzotriazol-5-yl} propanoate (1 eq., 855 mg, 1.3 mmol) was dissolved in THF (80 mL) and PPh<sub>3</sub> (3 eq., 1020 mg, 3.89 mmol) was added. DIAD (3 eq., 787 mg, 3.89 mmol) was added dropwise at RT and the mixture was stirred at RT for further 1.5h. After completion of the reaction the solvent was evaporated, the

15 crude product was purified via normal phase silica gel chromatography using heptane-AcOEt (100:0 to 35:65) as an eluent to give the title compound (white solid, quant.).

<sup>1</sup>H-NMR (500 MHz, DMSO-d<sub>6</sub>) δ ppm: 7.65 (d, 1 H), 7.46 (d, 1 H), 7.42 (dd, 1 H), 7.42 (s, 1 H), 7.23 (d, 1 H), 7.13 (d, 1 H), 6.61 (s, 1 H), 4.86 (m, 2 H), 4.78 (t, 1 H), 4.36/4.08 (d+d, 2 H), 4.21/3.9 (d+d, 2 H), 4.01/3.94 (m+m, 2 H), 3.97/3.86 (m+m, 2 H), 3.86 (q, 2 H), 3.85/3.62

20 (m+m, 2 H), 3.09/3.02 (dd+dd, 2 H), 2.74 (s, 3 H), 2.3 (s, 3 H), 0.96 (t, 3 H)

**STEP 5 : Preparation of EXAMPLE 75**

Using General Procedure 12 starting from ethyl [24-chloro-4,32-dimethyl-28,28-dioxo-19,22,27-trioxa-28λ<sup>6</sup>-thia-1,14,15,16-

25 tetraazahexacyclo[21.5.3.1<sup>3,7</sup>.1<sup>9,13</sup>.0<sup>12,16</sup>.0<sup>26,30</sup>]tritiaconta-3(33),4,6,9(32),10,12,14,23,25,30-decaen-8-yl]acetate (1 eq.) as a reactant, the title compound (white solid, 93% yield) was obtained.

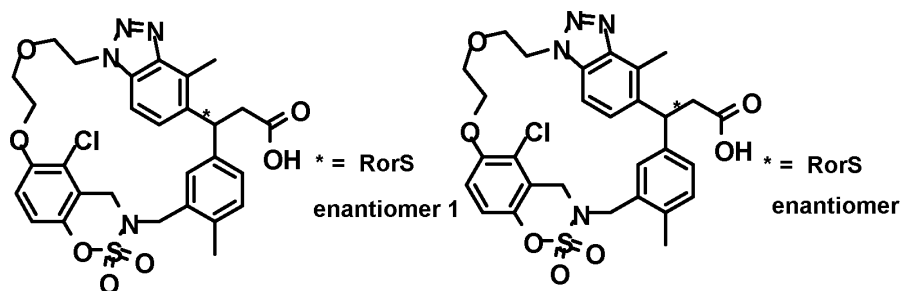
**HRMS** calculated for C<sub>29</sub>H<sub>29</sub>ClN<sub>4</sub>O<sub>7</sub>S: 612.1445; [M+H]<sup>+</sup> found: 613.1505 (δ = -2.2 ppm)

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**<sup>1</sup>H-NMR** (500 MHz, DMSO-d<sub>6</sub>) δ ppm: (m, 6 H), 12.08 (brs., 1 H), 7.65 (d, 1 H), 7.45 (d, 1 H), 7.43 (d, 1 H), 7.42 (s, 1 H), 7.23 (d, 1 H), 7.1 (s, 1 H), 6.6 (s, 1 H), 4.86 (m, 2 H), 4.76 (t, 1 H), 4.35/4.1 (d+d, 2 H), 4.2/3.9 (d+d, 2 H), 2.95 (d, 2 H), 2.74 (s, 3 H), 2.31 (s, 3 H)

**<sup>13</sup>C-NMR** (125 MHz, DMSO-d<sub>6</sub>) δ ppm: 173.1, 131.2, 130.8, 129.4, 126.8, 119.8, 116, 108.9, 71.3/69.9/68.3, 52, 48.6, 48.4, 41.7, 41.1, 18.6, 13.4

**EXAMPLE 76** : [31-Chloro-4,32-dimethyl-28,28-dioxo-19,22,27-trioxa-28λ<sup>6</sup>-thia-1,14,15,16-tetraazahexacyclo[21.5.3.1<sup>3,7</sup>.1<sup>9,13</sup>.0<sup>12,16</sup>.0<sup>26,30</sup>]tritiacont-3(33),4,6,9(32),10,12,14,23,25,30-decaen-8-yl]acetic acid



**STEP 1: Preparation of ethyl 3-(3-{[6-(benzyloxy)-5-chloro-2,2-dioxo-2H-1,2λ<sup>6</sup>,3-benzoxathiazin-3(4H)-yl]methyl}-4-methylphenyl)-3-(1-{2-[2-(benzyloxy)ethoxy]ethyl}-4-methyl-1H-benzotriazol-5-yl)propanoate**

Using General Procedure 6 starting from ethyl (E)-3-[1-[2-(2-benzyloxyethoxy)ethyl]-4-methyl-benzotriazol-5-yl]prop-2-enoate (1 eq.) and 6-benzyloxy-5-chloro-3-[[2-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]methyl]-4H-1,2λ<sup>6</sup>,3-benzoxathiazine 2,2-dioxide (1.2 eq.) as reactants, the title compound (white solid foam, 27% yield) was obtained.

**<sup>1</sup>H-NMR** (500 MHz, DMSO-d<sub>6</sub>) δ ppm: 7.59 (d, 1 H), 7.51-7.12 (m, 10 H), 7.42 (d, 1 H), 7.34 (d, 1 H), 7.24 (d, 1 H), 7.21 (dd, 1 H), 7.21 (d, 1 H), 7.14 (d, 1 H), 5.25 (s, 2 H), 4.83 (t, 1 H), 4.78 (t, 2 H), 4.4 (s, 2 H), 4.28 (s, 2 H), 4.24 (s, 2 H), 3.9 (q, 2 H), 3.87 (t, 2 H), 3.5 (m, 2 H), 3.4 (m, 2 H), 3.12 (m, 2 H), 2.75 (s, 3 H), 2.23 (s, 3 H), 0.98 (t, 3 H)

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**STEP 2 : Preparation of ethyl 3-{3-[(5-chloro-6-hydroxy-2,2-dioxo-2*H*-1,2λ<sup>6</sup>,3-benzoxathiazin-3(4*H*)-yl)methyl]-4-methylphenyl}-3-{1-[2-(2-hydroxyethoxy)ethyl]-4-methyl-1*H*-benzotriazol-5-yl}propanoate**

5 Using General Procedure 8 starting from ethyl 3-(3-{[6-(benzyloxy)-5-chloro-2,2-dioxo-2*H*-1,2λ<sup>6</sup>,3-benzoxathiazin-3(4*H*)-yl)methyl]-4-methylphenyl}-3-(1-{2-[2-(benzyloxy)ethoxy]ethyl]-4-methyl-1*H*-benzotriazol-5-yl}propanoate (1 eq.) as a reactant, the title compound (white solid foam, quant.) was obtained.

<sup>1</sup>H-NMR (500 MHz, DMSO-d<sub>6</sub>) δ ppm: 10.51 (s, 1 H), 7.6 (d, 1 H), 7.47 (d, 1 H), 7.25 (d, 1 H), 7.24 (dd, 1 H), 7.16 (d, 1 H), 7.05 (d, 1 H), 7.02 (d, 1 H), 4.84 (t, 1 H), 4.8 (t, 2 H), 4.54 (m, 1 H), 4.37 (s, 2 H), 4.24 (s, 2 H), 3.92 (q, 2 H), 3.88 (t, 2 H), 3.38 (m, 2 H), 3.38 (m, 2 H), 3.15 (m, 2 H), 2.76 (s, 3 H), 2.24 (s, 3 H), 1 (t, 3 H)

**STEP 3 : Preparation of ethyl [31-chloro-4,32-dimethyl-28,28-dioxo-19,22,27-trioxa-28λ<sup>6</sup>-thia-1,14,15,16-tetraazahexacyclo[21.5.3.1<sup>3,7</sup>.1<sup>9,13</sup>.0<sup>12,16</sup>.0<sup>26,30</sup>]tritriaconta-3(33),4,6,9(32),10,12,14,23,25,30-decaen-8-yl]acetate**

Ethyl 3-{3-[(5-chloro-6-hydroxy-2,2-dioxo-2*H*-1,2λ<sup>6</sup>,3-benzoxathiazin-3(4*H*)-yl)methyl]-4-methylphenyl}-3-{1-[2-(2-hydroxyethoxy)ethyl]-4-methyl-1*H*-benzotriazol-5-yl}propanoate (1 eq., 385 mg, 0.584 mmol) was dissolved in THF (10 mL) and PPh<sub>3</sub> (3 eq., 460 mg, 1.75 mmol) was added. DIAD (3 eq., 354 mg, 1.75 mmol) was added dropwise at RT and the mixture was stirred at this temperature for further 1.5h. After completion of the reaction the solvent was evaporated, the crude product was purified via normal phase silica gel chromatography using heptane-AcOEt (100:0 to 35:65) as an eluent to give the title compound (white solid foam, 64% yield).

<sup>1</sup>H-NMR (500 MHz, DMSO-d<sub>6</sub>) δ ppm: 7.59 (d, 1 H), 7.47 (dd, 1 H), 7.32 (d, 1 H), 7.29 (d, 1 H), 7.09 (d, 1 H), 7.07 (d, 1 H), 6.61 (d, 1 H), 4.83 (m, 2 H), 4.78 (t, 1 H), 4.28/3.9 (d+d, 2 H), 4.21/4.03 (d+d, 2 H), 4.17-3.98 (m, 4 H), 3.9 (m, 2 H), 3.76 (m, 2 H), 3.04/2.99 (dd+dd, 2 H), 2.59 (s, 3 H), 2.34 (s, 3 H), 0.99 (t, 3 H)

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**STEP 4 : Preparation of EXAMPLE 76**

Using General Procedure 12 starting from ethyl [31-chloro-4,32-dimethyl-28,28-dioxo-19,22,27-trioxa-28 $\lambda^6$ -thia-1,14,15,16-tetraazahexacyclo[21.5.3.1<sup>3,7</sup>.1<sup>9,13</sup>.0<sup>12,16</sup>.0<sup>26,30</sup>]

- 5 tritriaconta-3(33),4,6,9(32),10,12,14,23,25,30-decaen-8-yl]acetate (1 eq.) as a reactant, the title compound (white solid, 86% yield) was obtained.

The enantiopure products were obtained by chromatographic separation on chiral column.

**Example 76a (E1)**

- 10 **HRMS** calculated for C<sub>29</sub>H<sub>29</sub>ClN<sub>4</sub>O<sub>7</sub>S: 612.1445; [M+H]<sup>+</sup> found: 613.1499 ( $\delta$  = -3.1 ppm)

**Example 76b (E2)**

**HRMS** calculated for C<sub>29</sub>H<sub>29</sub>ClN<sub>4</sub>O<sub>7</sub>S: 612.1445; [M+H]<sup>+</sup> found: 613.1515 ( $\delta$  = -0.5 ppm)

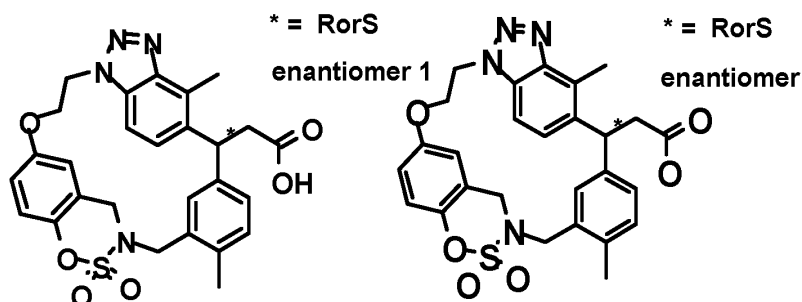
- <sup>1</sup>H-NMR** (500 MHz, DMSO-d<sub>6</sub>)  $\delta$  ppm: 11.83 (brs, 1 H), 7.59 (d, 1 H), 7.49 (dd, 1 H), 7.33  
15 (d, 1 H), 7.29 (d, 1 H), 7.1 (d, 1 H), 7.07 (d, 1 H), 6.58 (d, 1 H), 4.85/4.8 (m+m, 2 H), 4.75 (t, 1 H), 4.26/3.89 (d+d, 2 H), 4.2/4.03 (d+d, 2 H), 4.14/4.09 (m+m, 2 H), 4.09/4.01 (m+m, 2 H), 3.77 (m, 2 H), 2.88/2.82 (dd+dd, 2 H), 2.58 (s, 3 H), 2.34 (s, 3 H)

**<sup>13</sup>C-NMR** (125 MHz, DMSO-d<sub>6</sub>)  $\delta$  ppm: 131.6, 130.7, 129.5, 126.8, 117.1, 114.4, 108.5, 69.5, 68.9, 68.3, 52.2, 48.8, 47.4, 42.1, 41.9, 18.5, 13.3

20

**EXAMPLE 77** : [4,29-Dimethyl-25,25-dioxo-19,24-dioxa-25 $\lambda^6$ -thia-1,14,15,16-tetraazahexacyclo[18.5.3.1<sup>3,7</sup>.1<sup>9,13</sup>.0<sup>12,16</sup>.0<sup>23,27</sup>]triaconta-3(30),4,6,9(29),10,12,14,20,22,27-decaen-8-yl]acetic acid

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**STEP 1 : Preparation of ethyl [4,29-dimethyl-25,25-dioxo-19,24-dioxa-25 $\lambda^6$ -thia-1,14,15,16-tetraazahexacyclo[18.5.3.1<sup>3,7</sup>.1<sup>9,13</sup>.0<sup>12,16</sup>.0<sup>23,27</sup>]triaconta-3(30),4,6,9(29),10,12,14,20,22,27-decaen-8-yl]acetate**

Ethyl 3-{3-[(6-hydroxy-2,2-dioxo-2*H*-1,2 $\lambda^6$ ,3-benzoxathiazin-3(4*H*)-yl)methyl]-4-methylphenyl}-3-[1-(2-hydroxyethyl)-4-methyl-1*H*-benzotriazol-5-yl]propanoate (1 eq., 320 mg, 0.5512 mmol) was dissolved in THF (60 mL) and PPh<sub>3</sub> (2 eq., 289 mg, 1.10 mmol) was added. DIAD (2 eq., 0.217 mL, 222.86 mg, 1.1 mmol) was added to the stirred solution and the reaction mixture was stirred at 70 °C for 2h. The mixture was concentrated under reduced pressure and the residue was purified by reversed-phase chromatography using 5 mM aq. NH<sub>4</sub>HCO<sub>3</sub>-MeCN gradient elution to give the title compound (230 mg, 74% yield) as a white solid foam.

**<sup>1</sup>H-NMR** (500 MHz, DMSO-*d*<sub>6</sub>)  $\delta$  ppm: 7.79 (d, 1 H), 7.51 (dd, 1 H), 7.36 (d, 1 H), 7.3 (d, 1 H), 6.92 (d, 1 H), 6.87 (dd, 1 H), 5.89 (d, 1 H), 5.88 (d, 1 H), 5.15/5.04 (m+m, 2 H), 4.79 (dd, 1 H), 4.68/4.33 (m+m, 2 H), 4.15/3.54 (d+d, 2 H), 3.98/3.69 (d+d, 2 H), 3.94/3.91 (m+m, 2 H), 3.43/3.04 (dd+dd, 2 H), 2.61 (s, 3 H), 2.29 (s, 3 H), 0.99 (t, 3 H)

**STEP 2 : Preparation of EXAMPLE 77**

Using General Procedure 12 starting from ethyl [4,29-dimethyl-25,25-dioxo-19,24-dioxa-25 $\lambda^6$ -thia-1,14,15,16-tetraazahexacyclo[18.5.3.1<sup>3,7</sup>.1<sup>9,13</sup>.0<sup>12,16</sup>.0<sup>23,27</sup>]triaconta-

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3(30),4,6,9(29),10,12,14,20,22,27-decaen-8-yl]acetate (1 eq., 265 mg, 0.4710 mmol) as a reactant, gave the title compound (175 mg, 69% yield).

The enantiopure products were obtained by chromatographic separation on chiral column.

#### 5 **Example 77a (E1)**

**HRMS** calculated for  $C_{27}H_{26}N_4O_6S$ : 534.1573;  $[M+H]^+$  found: 535.1646 ( $\delta = 0.0$  ppm)

#### **Example 77b (E2)**

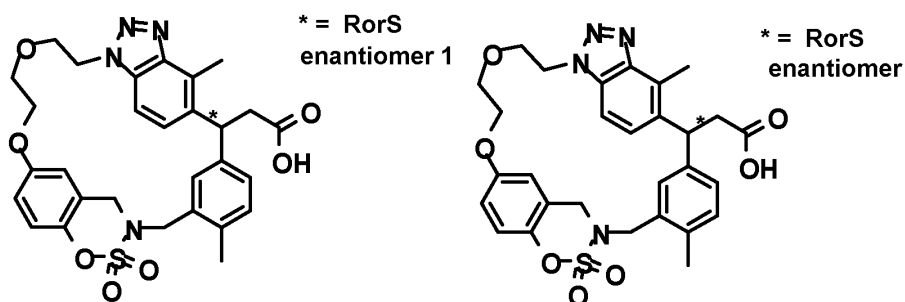
**HRMS** calculated for  $C_{27}H_{26}N_4O_6S$ : 534.1573;  $[M+H]^+$  found: 535.1646 ( $\delta = 0.0$  ppm)

10  **$^1H$ -NMR** (500 MHz, DMSO- $d_6$ )  $\delta$  ppm: 12.21 (brs, 1 H), 7.79 (d, 1 H), 7.51 (dd, 1 H), 7.34 (d, 1 H), 7.3 (d, 1 H), 6.92 (d, 1 H), 6.87 (dd, 1 H), 5.88 (d, 1 H), 5.88 (d, 1 H), 5.15/5.03 (m+m, 2 H), 4.77 (t, 1 H), 4.67/4.34 (m+m, 2 H), 4.14/3.55 (d+d, 2 H), 3.97/3.7 (d+d, 2 H), 3.31/2.94 (dd+dd, 2 H), 2.6 (s, 3 H), 2.29 (s, 3 H)

15  **$^{13}C$ -NMR** (125 MHz, DMSO- $d_6$ )  $\delta$  ppm: 132.2, 131.2, 127.8, 127.1, 118.9, 116.4, 115.7, 109.8, 69.8, 51.6, 49.2, 48, 40.1, 40, 18.1, 13.1

**EXAMPLE 78:** [4,32-Dimethyl-28,28-dioxo-19,22,27-trioxa-28 $\lambda^6$ -thia-1,14,15,16-tetraazahexacyclo[21.5.3.1<sup>3,7</sup>.1<sup>9,13</sup>.0<sup>12,16</sup>.0<sup>26,30</sup>]tritiaconta-3(33),4,6,9(32),10,12,14,23,25,30-decaen-8-yl]acetic acid

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**STEP 1 : Preparation of ethyl 3-(3-{[6-(benzyloxy)-2,2-dioxo-2*H*-1,2λ<sup>6</sup>,3-benzoxathiazin-3(4*H*)-yl]methyl}-4-methylphenyl)-3-(1-{2-[2-(benzyloxy)ethoxy]ethyl}-4-methyl-1*H*-benzotriazol-5-yl)propanoate**

5 Using General Procedure 7 starting from ethyl 3-(1-{2-[2-(benzyloxy)ethoxy]ethyl}-4-methyl-1*H*-benzotriazol-5-yl)-3-[3-(hydroxymethyl)-4-methylphenyl]propanoate (1 eq., 2.19 g, 4.12 mmol) and 6-(benzyloxy)-3,4-dihydro-2*H*-1,2λ<sup>6</sup>,3-benzoxathiazine-2,2-dione (1.2 eq., 1.44 g, 4.94 mmol) as reactants, the title compound (2.604 g, 79% yield) was obtained.

<sup>1</sup>H-NMR (500 MHz, DMSO-d<sub>6</sub>) δ ppm: (m, 5 H), (m, 5 H), 7.6 (d, 1 H), 7.43 (d, 1 H), 7.21  
10 (d, 1 H), 7.16 (dd, 1 H), 7.14 (d, 1 H), 7.11 (d, 1 H), 7.07 (dd, 1 H), 6.95 (d, 1 H), 5.1 (s, 2 H), 4.83 (t, 1 H), 4.78 (t, 2 H), 4.43/4.39 (d+d, 2 H), 4.28 (s, 2 H), 4.21/4.18 (d+d, 2 H), 3.91 (q, 2 H), 3.86 (t, 2 H), 3.49 (m, 2 H), 3.4 (m, 2 H), 3.17/3.11 (dd+dd, 2 H), 2.75 (s, 3 H), 2.2 (s, 3 H), 0.98 (t, 3 H)

15 **STEP 2 : Preparation of ethyl 3-{3-[(6-hydroxy-2,2-dioxo-2*H*-1,2λ<sup>6</sup>,3-benzoxathiazin-3(4*H*)-yl)methyl]-4-methylphenyl}-3-{1-[2-(2-hydroxyethoxy)ethyl]-4-methyl-1*H*-benzotriazol-5-yl}propanoate**

Using General Procedure 8 starting from ethyl 3-(3-{[6-(benzyloxy)-2,2-dioxo-2*H*-1,2λ<sup>6</sup>,3-benzoxathiazin-3(4*H*)-yl]methyl}-4-methylphenyl)-3-(1-{2-[2-(benzyloxy)ethoxy]ethyl}-4-methyl-1*H*-benzotriazol-5-yl)propanoate (1 eq., 2.60 mg, 3.23 mmol) as a reactant, the title  
20 compound (2.604 g, 79% yield) was obtained.

<sup>1</sup>H-NMR (500 MHz, DMSO-d<sub>6</sub>) δ ppm: 9.71 (s, 1 H), 7.63 (d, 1 H), 7.49 (d, 1 H), 7.23 (d, 1 H), 7.19 (dd, 1 H), 7.13 (d, 1 H), 6.99 (d, 1 H), 6.79 (dd, 1 H), 6.61 (d, 1 H), 4.84 (t, 1 H), 4.8  
25 (t, 2 H), 4.54 (m, 1 H), 4.4/4.36 (d+d, 2 H), 4.22/4.17 (d+d, 2 H), 3.94 (q, 2 H), 3.88 (t, 2 H), 3.38 (m, 2 H), 3.37 (m, 2 H), 3.17 (m, 2 H), 2.76 (s, 3 H), 2.22 (s, 3 H), 1.01 (t, 3 H)

**STEP 3 : Preparation of ethyl [4,32-dimethyl-28,28-dioxo-19,22,27-trioxa-28λ<sup>6</sup>-thia-1,14,15,16-tetraazahexacyclo[21.5.3.1<sup>3,7</sup>.1<sup>9,13</sup>.0<sup>12,16</sup>.0<sup>26,30</sup>]tritiaconta-3(33),4,6,9(32),10,12,14,23,25,30-decaen-8-yl]acetate**

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Using General Procedure 7 starting from ethyl 3-{3-[(6-hydroxy-2,2-dioxo-2*H*-1,2λ<sup>6</sup>,3-benzoxathiazin-3(4*H*)-yl)methyl]-4-methylphenyl}-3-{1-[2-(2-hydroxyethoxy)ethyl]-4-methyl-1*H*-benzotriazol-5-yl}propanoate (1 eq., 2.10 mg, 3.36 mmol) as a reactant in 120 mL/mmol THF, the title compound (1.65 g, 81% yield) was obtained.

<sup>1</sup>H-NMR (500 MHz, DMSO-d<sub>6</sub>) δ ppm: (m, 6 H), 7.73 (d, 1 H), 7.44 (d, 1 H), 7.43 (dd, 1 H), 7.25 (d, 1 H), 7.06 (d, 1 H), 6.92 (dd, 1 H), 6.81 (d, 1 H), 6.46 (d, 1 H), 4.84 (m, 2 H), 4.81 (t, 1 H), 4.27/4.06 (d+d, 2 H), 4.15/4.07 (d+d, 2 H), 3.88 (q, 2 H), 3.08/3.03 (dd+dd, 2 H), 2.67 (s, 3 H), 2.32 (s, 3 H), 0.97 (t, 3 H)

#### STEP 4 : Preparation of EXAMPLE 78

Using General Procedure 12 starting from ethyl [4,32-dimethyl-28,28-dioxo-19,22,27-trioxo-28λ<sup>6</sup>-thia-1,14,15,16-tetraazahexacyclo[21.5.3.1<sup>3,7</sup>.1<sup>9,13</sup>.0<sup>12,16</sup>.0<sup>26,30</sup>]tritiaconta-3(33),4,6,9(32),10,12,14,23,25,30-decaen-8-yl]acetate (1 eq., 1.645 g, 2.72 mmol) as a reactant, the title compound was obtained (83% yield).

The enantiopure products were obtained by chromatographic separation on chiral column.

#### Example 78a (E1)

HRMS calculated for C<sub>29</sub>H<sub>30</sub>N<sub>4</sub>O<sub>7</sub>S: 578.1835; [M+H]<sup>+</sup> found: 579.1915 (δ = 1.2 ppm)

#### Example 78b (E2)

HRMS calculated for C<sub>29</sub>H<sub>30</sub>N<sub>4</sub>O<sub>7</sub>S: 578.1835; [M+H]<sup>+</sup> found: 579.1917 (δ = 1.6 ppm)

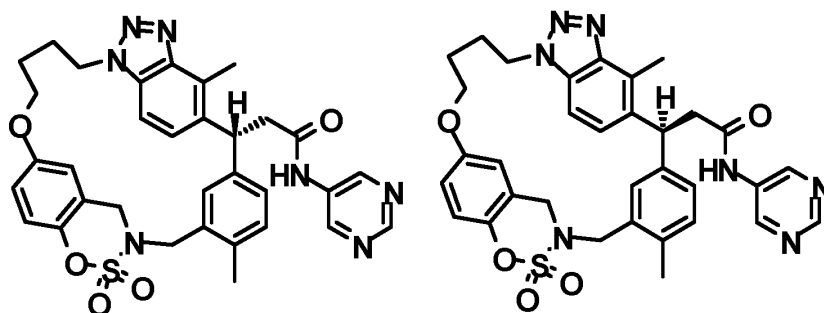
<sup>1</sup>H-NMR (500 MHz, DMSO-d<sub>6</sub>) δ ppm: 12.28 (brs, 1 H), 7.72 (d, 1 H), 7.43 (dd, 1 H), 7.42 (d, 1 H), 7.25 (d, 1 H), 7.06 (d, 1 H), 6.92 (dd, 1 H), 6.78 (d, 1 H), 6.44 (d, 1 H), 4.85/4.82 (m+m, 2 H), 4.79 (t, 1 H), 4.25/4.05 (d+d, 2 H), 4.15/4.06 (d+d, 2 H), 4.03/3.98 (m+m, 2 H), 4 (m, 2 H), 3.8/3.74 (m+m, 2 H), 2.93 (d, 2 H), 2.66 (s, 3 H), 2.32 (s, 3 H)

<sup>13</sup>C-NMR (125 MHz, DMSO-d<sub>6</sub>) δ ppm: 131.4, 130.7, 129.4, 127.2, 118.9, 115.3, 114.7, 109, 69.8, 68.5, 68.4, 51.8, 49, 48.4, 41.8, 41.7, 18.5, 13.3

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**EXAMPLE 79** : 2-[(8*R*)-4,31-Dimethyl-27,27-dioxo-21,26-dioxa-27 $\lambda^6$ -thia-1,14,15,16-tetraazahexacyclo[20.5.3.1<sup>3,7</sup>.1<sup>9,13</sup>.0<sup>12,16</sup>.0<sup>25,29</sup>]dotriaconta-3(32),4,6,9(31),10,12,14,22,24,29-decaen-8-yl]-*N*-(pyrimidin-5-yl)acetamide and

5 2-[(8*S*)-4,31-dimethyl-27,27-dioxo-21,26-dioxa-27 $\lambda^6$ -thia-1,14,15,16-tetraazahexacyclo[20.5.3.1<sup>3,7</sup>.1<sup>9,13</sup>.0<sup>12,16</sup>.0<sup>25,29</sup>]dotriaconta-3(32),4,6,9(31),10,12,14,22,24,29-decaen-8-yl]-*N*-(pyrimidin-5-yl)acetamide



10

To a stirred solution of [(8*R*)-4,31-dimethyl-27,27-dioxo-21,26-dioxa-27 $\lambda^6$ -thia-1,14,15,16-tetraazahexacyclo[20.5.3.1<sup>3,7</sup>.1<sup>9,13</sup>.0<sup>12,16</sup>.0<sup>25,29</sup>]dotriaconta-3(32),4,6,9(31),10,12,14,22,24,29-decaen-8-yl]acetic acid or [(8*S*)-4,31-dimethyl-27,27-dioxo-21,26-dioxa-27 $\lambda^6$ -thia-1,14,15,16-tetraazahexacyclo[20.5.3.1<sup>3,7</sup>.1<sup>9,13</sup>.0<sup>12,16</sup>.0<sup>25,29</sup>]dotriaconta-3(32),4,6,9(31),10,12,14,22,24,29-decaen-8-yl]acetic acid (1 eq., 250 mg, 0.444 mmol) in dry DMF (3 mL) 1-  
15 [bis(dimethylamino)methylene]-1*H*-1,2,3-triazolo[4,5-*b*]pyridinium 3-oxide hexafluorophosphate (1.48 eq., 250 mg, 0.657 mmol) and DIPEA (3.2 eq., 0.25 mL, 1.4 mmol) were added at RT. The mixture was stirred at RT for 3 min, then pyrimidin-5-amine (2.37 eq.,  
20 100 mg, 1.05 mmol) was added and the mixture was stirred overnight at RT. After completion of the reaction the mixture was filtered, the filtrate was diluted with DMF and purified by reversed-phase chromatography using aq. 25 mM NH<sub>4</sub>HCO<sub>3</sub> solution-MeCN as eluents to give the title compound (white solids, 48% yield).

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**Example 79a (8R)**

**HRMS** calculated for  $C_{33}H_{33}N_7O_5S$ : 639.2264;  $[M+H]^+$  found: 640.2335 ( $\delta = -0.3$  ppm)

**Example 79b (8S)**

5 **HRMS** calculated for  $C_{33}H_{33}N_7O_5S$ : 639.2264;  $[M+H]^+$  found: 640.2332 ( $\delta = -0.7$  ppm)

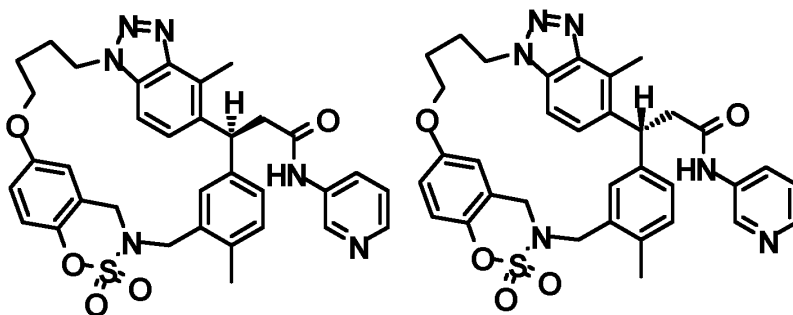
**$^1H$ -NMR** (500 MHz, DMSO- $d_6$ )  $\delta$  ppm: 10.45 (s, 1 H), 8.88 (s, 2 H), 8.83 (s, 1 H), 7.68 (d, 1 H), 7.52 (dd, 1 H), 7.43 (d, 1 H), 7.31 (d, 1 H), 7 (d, 1 H), 6.8 (dd, 1 H), 6.54 (d, 1 H), 5.82 (d, 1 H), 4.94 (t, 1 H), 4.78/4.73 (m+m, 2 H), 4.11/3.98 (d+d, 2 H), 3.99/3.87 (d+d, 2 H), 3.61/3.4 (m+m, 2 H), 3.24/3.11 (dd+dd, 2 H), 2.63 (s, 3 H), 2.33 (s, 3 H), 2.2/2.08 (m+m, 2 H), 1.82/1.62 (m+m, 2 H)

10  **$^{13}C$ -NMR** (125 MHz, DMSO- $d_6$ )  $\delta$  ppm: 153.5, 147.4, 131.5, 131.3, 128.4, 127.4, 119.6, 117.5, 111.2, 108.1, 67.9, 51.9, 48.8, 48.3, 42.7, 41.7, 26.7, 25.5, 18.5, 13.5

**EXAMPLE 80 : 2-[(8S)-4,31-Dimethyl-27,27-dioxo-21,26-dioxa-27 $\lambda^6$ -thia-1,14,15,16-**

15 **tetraazahexacyclo[20.5.3.1 $^{3,7}$ .1 $^{9,13}$ .0 $^{12,16}$ .0 $^{25,29}$ ]dotriaconta-3(32),4,6,9(31),10,12,14,22,24,29-decaen-8-yl]-N-(pyridin-3-yl)acetamide and**

20 **2-[(8R)-4,31-dimethyl-27,27-dioxo-21,26-dioxa-27 $\lambda^6$ -thia-1,14,15,16-tetraazahexacyclo[20.5.3.1 $^{3,7}$ .1 $^{9,13}$ .0 $^{12,16}$ .0 $^{25,29}$ ]dotriaconta-3(32),4,6,9(31),10,12,14,22,24,29-decaen-8-yl]-N-(pyridin-3-yl)acetamide**



To a stirred solution of [(8S)-4,31-dimethyl-27,27-dioxo-21,26-dioxa-27 $\lambda^6$ -thia-1,14,15,16-tetraazahexacyclo[20.5.3.1 $^{3,7}$ .1 $^{9,13}$ .0 $^{12,16}$ .0 $^{25,29}$ ]dotriaconta-3(32),4,6,9(31),10,12,14,22,24,29-

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decaen-8-yl]acetic acid or [(8R)-4,31-dimethyl-27,27-dioxo-21,26-dioxa-27 $\lambda^6$ -thia-1,14,15,16-tetraazahexacyclo[20.5.3.1<sup>3,7</sup>.1<sup>9,13</sup>.0<sup>12,16</sup>.0<sup>25,29</sup>]dotriaconta-3(32),4,6,9(31),10,12,14,22,24,29-decaen-8-yl]acetic acid (1 eq., 250 mg, 0.444 mmol) in dry DMF (3 mL) 1-bis(dimethylamino)methylene]-1H-1,2 $\lambda$ 6,3-triazolo[4,5-b]pyridinium 3-oxide hexafluorophosphate (1.48 eq., 250 mg, 0.657 mmol) and DIPEA (3.2 eq., 0.25 mL, 1.4 mmol) were added at RT. The mixture was stirred at RT for 3 min, then pyridin-3-amine (2.39 eq., 100 mg, 1.06 mmol) was added and the mixture was stirred overnight at RT. After completion of the reaction the mixture was filtered, the filtrate was diluted with DMF and purified by reversed-phase chromatography using aq. 25 mM NH<sub>4</sub>HCO<sub>3</sub> solution-MeCN as eluents to give the title compound (white solids, 44% yield).

**Example 80a (8S)**

HRMS calculated for C<sub>34</sub>H<sub>34</sub>N<sub>6</sub>O<sub>5</sub>S: 638.2311; [M+H]<sup>+</sup> found: 639.2382 ( $\delta$  = -0.3 ppm)

15 **Example 80b (8R)**

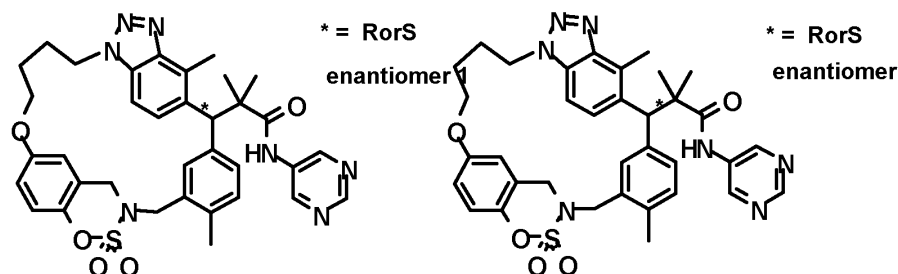
HRMS calculated for C<sub>34</sub>H<sub>34</sub>N<sub>6</sub>O<sub>5</sub>S: 638.2311; [M+H]<sup>+</sup> found: 639.2381 ( $\delta$  = -0.5 ppm)

<sup>1</sup>H-NMR (500 MHz, DMSO-d<sub>6</sub>)  $\delta$  ppm: 10.22 (s, 1 H), 8.6 (s, 1 H), 8.2 (dd, 1 H), 7.91 (dm, 1 H), 7.68 (d, 1 H), 7.53 (dd, 1 H), 7.42 (d, 1 H), 7.31 (d, 1 H), 7.27 (m, 1 H), 7 (d, 1 H), 6.8 (dd, 1 H), 6.53 (d, 1 H), 5.83 (d, 1 H), 4.94 (t, 1 H), 4.77/4.74 (m+m, 2 H), 4.1/3.98 (d+d, 2 H), 3.99/3.88 (d+d, 2 H), 3.62/3.41 (m+m, 2 H), 3.21/3.08 (dd+dd, 2 H), 2.63 (s, 3 H), 2.33 (s, 3 H), 2.2/2.07 (m+m, 2 H), 1.82/1.62 (m+m, 2 H)

<sup>13</sup>C-NMR (125 MHz, DMSO-d<sub>6</sub>)  $\delta$  ppm: 144.6, 141, 131.4, 131.3, 128.4, 127.4, 126.4, 124.1, 119.5, 117.5, 111.2, 108, 67.8, 51.9, 48.8, 48.3, 42.8, 41.7, 26.7, 25.5, 18.5, 13.4

25 **EXAMPLE 81 : 2-[4,31-Dimethyl-27,27-dioxido-21,26-dioxa-27-thia-1,14,15,16-tetraazahexacyclo[20.5.3.1<sup>3,7</sup>.1<sup>9,13</sup>.0<sup>12,16</sup>.0<sup>25,29</sup>]dotriaconta-3(32),4,6,9(31),10,12,14,22,24,29-decaen-8-yl]-2-methyl-N-(pyrimidin-5-yl)propanamide**

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The stirred solution of 2-[4,31-dimethyl-27,27-dioxido-21,26-dioxa-27-thia-1,14,15,16-tetraazahexacyclo[20.5.3.1<sup>3,7</sup>.1<sup>9,13</sup>.0<sup>12,16</sup>.0<sup>25,29</sup>]dotriaconta-3(32),4,6,9(31),10,12,14,22,24,29-decaen-8-yl]-2-methylpropanoic acid E1 (1 eq., 261 mg, 0.442 mmol) or E2 (1 eq.) in thionyl chloride (310 eq., 16.3 g, 10 mL, 0.137 mol) was heated under N<sub>2</sub> atmosphere at 80 °C for 1 day. After completion of the reaction, the mixture was evaporated to dryness and used without further purification. The crude acyl chloride was dissolved in THF (5 mL), then DIPEA (44 mg, 0.442 mmol) and pyrimidin-5-amine (42 mg, 0.442 mmol) were added and the mixture was stirred overnight at RT. After completion of the reaction the mixture was purified directly by reversed-phase chromatography using aq. 5 mM NH<sub>4</sub>HCO<sub>3</sub> solution-MeCN as eluents to give the title compound (white solids, 14%- 15% yields respectively).

#### Example 81a (E1)

HRMS calculated for C<sub>35</sub>H<sub>37</sub>N<sub>7</sub>O<sub>5</sub>S: 667.2577; [M+H]<sup>+</sup> found: 668.2657 (δ = 1.1 ppm)

#### Example 81b (E2)

HRMS calculated for C<sub>35</sub>H<sub>37</sub>N<sub>7</sub>O<sub>5</sub>S: 667.2577; [M+H]<sup>+</sup> found: 668.2654 (δ = 0.7 ppm)

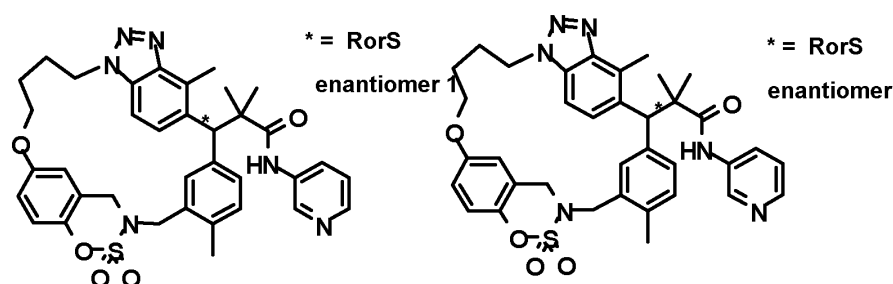
<sup>1</sup>H-NMR (500 MHz, DMSO-d<sub>6</sub>) δ ppm: 9.71 (brs., 1 H), 8.81 (s, 1 H), 8.76 (s, 2 H), 7.63 (d, 1 H), 7.57 (d, 1 H), 7.46 (brd., 1 H), 7.29 (d, 1 H), 7.01 (d, 1 H), 6.81 (dd, 1 H), 6.67 (brs., 1 H), 5.75 (brs., 1 H), 5.03 (s, 1 H), 4.76/4.7 (dm+dm, 2 H), 4.43/3.75 (brd+brd, 2 H), 4.13/3.57 (brd+brd, 2 H), 3.66/3.35 (br+m, 2 H), 2.65 (brs., 3 H), 2.34 (s, 3 H), 2.18/2.06 (m+m, 2 H), 1.83/1.67 (m+m, 2 H), 1.38/1.23 (s+s, 6 H)

<sup>13</sup>C-NMR (125 MHz, DMSO-d<sub>6</sub>) δ ppm: 176.9, 153.8, 149, 133.2, 131.2, 130.8, 128, 119.6, 117.7, 110.8, 107, 67.9, 52, 52, 48.8, 48.2, 47, 26.8, 26.2/24.1, 25.6, 18.5, 14.2

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**EXAMPLE 82** : 2-[4,31-Dimethyl-27,27-dioxo-21,26-dioxa-27 $\lambda^6$ -thia-1,14,15,16-tetraazahexacyclo[20.5.3.1<sup>3,7</sup>.1<sup>9,13</sup>.0<sup>12,16</sup>.0<sup>25,29</sup>]dotriaconta-3(32),4,6,9(31),10,12,14,22,24,29-decaen-8-yl]-2-methyl-N-(pyridin-3-yl)propanamide

5



The stirred solution of 2-[4,31-dimethyl-27,27-dioxo-21,26-dioxa-27 $\lambda^6$ -thia-1,14,15,16-tetraazahexacyclo[20.5.3.1<sup>3,7</sup>.1<sup>9,13</sup>.0<sup>12,16</sup>.0<sup>25,29</sup>]dotriaconta-3(32),4,6,9(31),10,12,14,22,24,29-decaen-8-yl]-2-methylpropanoic acid E1 (1 eq., 261 mg, 0.442 mmol) or E2 (1 eq.) in thionyl chloride (310 eq., 16.3 g, 10 mL, 0.137 mol) was heated under N<sub>2</sub> atmosphere at 80 °C for 1 day. After completion of the reaction, the mixture was evaporated to dryness and used without further purification. The crude acyl chloride was dissolved in THF (5 mL), then DIPEA (44 mg, 0.442 mmol) and pyridin-3-amine (42 mg, 0.443 mmol) were added and the mixture was stirred overnight at RT. After completion of the reaction the mixture was purified directly by reversed-phase chromatography using aq. 5 mM NH<sub>4</sub>HCO<sub>3</sub> solution-MeCN eluents to give the title compound (white solids, 41%- 46% yields respectively).

**Example 82a (E1)**

20 **HRMS** calculated for C<sub>36</sub>H<sub>38</sub>N<sub>6</sub>O<sub>5</sub>S: 666.2625; [M+H]<sup>+</sup> found: 667.2697 ( $\delta$  = 0.0 ppm)

**Example 82b (E2)**

**HRMS** calculated for C<sub>36</sub>H<sub>38</sub>N<sub>6</sub>O<sub>5</sub>S: 666.2625; [M+H]<sup>+</sup> found: 667.2700 ( $\delta$  = 0.4 ppm)

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<sup>1</sup>H-NMR (500 MHz, DMSO-d<sub>6</sub>) δ ppm: 9.48 (s, 1 H), 8.51 (d, 1 H), 8.18 (d, 1 H), 7.75 (d, 1 H), 7.63 (d, 1 H), 7.57 (d, 1 H), 7.47 (d, 1 H), 7.29 (d, 1 H), 7.24 (dd, 1 H), 7.01 (d, 1 H), 6.81 (dd, 1 H), 6.65 (br, 1 H), 5.74 (br, 1 H), 5.05 (s, 1 H), 4.75/4.71 (m+m, 2 H), 4.43/3.74 (d+d, 2 H), 4.13/3.57 (d+d, 2 H), 3.66/3.34 (m+m, 2 H), 2.65 (s, 3 H), 2.34 (s, 3 H), 2.18/2.07 (m+m, 2 H), 1.83/1.67 (m+m, 2 H), 1.37 (s, 3 H), 1.22 (s, 3 H)

<sup>13</sup>C-NMR (125 MHz, DMSO-d<sub>6</sub>) δ ppm: 176.4, 156, 146.6, 144.9, 144.6, 142.8, 139.4, 136.4, 135.9, 135.6, 133.3, 131.8, 131.8, 131.2, 130.7, 128.7, 128.3, 128.1, 123.8, 119.6, 117.7, 117.1, 110.8, 107, 67.9, 52.1, 51.8, 48.8, 48.2, 46.9, 26.8, 26.3, 25.6, 24, 18.6, 14.2

### 10 **EXAMPLE 83 : HepG2 – Gene reporter assay**

Nrf2 transcription factor will activate protective genes from oxidative damage through the binding on the Antioxidant Response Elements (ARE). We used the transfection factor property of Nrf2 to develop a gene reporter assay, based on the activation of the betalactamase reporter gene under the control of the ARE and Nrf2 activation.

The CellSensor® ARE-bla HepG2 cell line (Ref.K1208, Invitrogen) containing a beta-lactamase reporter gene under control of the Antioxidant Response Element (ARE) was stably integrated into HepG2 cells.

CellSensor® ARE-bla HepG2 cells were grown to confluence in DMEM GlutaMAX™ (Ref.61965-026, Thermo Fisher), 10% dialyzed FBS (Ref.P30-193306, PanBiotech), 12mM Hepes (Ref.15630-056, Gibco), 0.1mM Non-Essential Amino Acid (NEAA) Cell Culture Supplement (Ref.11140-35, Gibco), 1% Na-pyruvate (Ref.S8636, Sigma), 2.5µg/ml Blasticidine (Ref.210-01, Invitrogen), 1% Pénicilline/ streptomycine (15070-063, Gibco) in collagen I (50µg/mL, Ref.A10483-1, Life Technologies) coated flasks, 37°C, 5% CO<sub>2</sub>.

Eighteen hours before the experiment, cells were harvested using Tryple Xpress (Ref.126905, Bibco) for 10min at 37°C, resuspended in DMEM GlutaMAX™ (Ref.61965-026, Thermo Fisher), 1% dialyzed FBS (Ref.P30-193306, PanBiotech), 25mM Hepes (Ref.15630-056, Gibco), 0.1mM NEAA (Ref.11140-35, Gibco), 1% Na-pyruvate (Ref.S8636, Sigma), 2.5µg/ml Blasticidine (Ref.210-01, Invitrogen), 1% Pénicilline/ streptomycine (15070-063, Gibco) then



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plated into 384 wells Cell culture microclear plates (Ref.781091, Greiner) at the density of 30 000 cells/well in 32µl. Cell are stored at 37°C, 5% CO<sub>2</sub> until used.

Compounds in 100% DMSO (0.315µl/well) were resuspended in 20µl DMEM GlutaMAX™, 1% dialyzed FBS, 25mM Hepes, 0.1mM NEAA, 1% Na-pyruvate (Ref.S8636, Sigma), 2.5µg/ml Blasticidine, 3.4% DMSO, 1% Pénicilline/ streptomycine (15070-063, Gibco). Compounds and andrographolide (10µM final concentration; Ref.365645-500MG, Aldrich)) as positive control, were dispensed on cell, 8µl/well, and then incubated for 16h at 37°C and 5% CO<sub>2</sub>. The day after Live Blazer reagent (Live Blazer FRET B/G (CCF4-AM), Ref.K1089, Invitrogen), was dispensed on cells (8 µl/well) and incubated for 2h at room temperature in the dark.

Then, Fluorescence Resonance Energy Transfer (FRET) signal was measured using multimodal reader (Ex 409nM/Em 460nM and 530 nM; Envision, Perkin Elmer). Data were normalized between 1% DMSO (basal signal) and 10µM andrographolide (positive signal) and analyzed using Activity Base software.

#### **EXAMPLE 84 : U2OS – translocation assay**

U2OS cell have been stably transduced using MMLV-derived retroviral vector, to overexpress Nrf2-Enzyme Donor fusion protein, and Acceptor Enzyme in the nucleus (PathHunter® U2OS Keap1-NRF2 Nuclear Translocation Cell Line, Ref.93-0821C3, DiscoverX).

PathHunter U2OS cells were grown in Minimum Essential Medium (MEM) (Ref.30-2003, ATCC), 10% FBS (Ref.P30-193306, PanBiotech), 500µg/ml Geneticine, 250µg/ml hygromycine, 0.25µg/ml puromycine (10131-027, 10687-010 and Ref.A1113802 respectively, Life Technologies).

The night before experiment, cells were harvested using Tryple Xpress (Ref.126905, Bibco) for 5min at 37°C, resuspended in Opti-MEM™ (Ref.31985-047, Gibco), 1% FBS (Ref.P30-193306, PanBiotech) and then plated into 384 wells plates (Ref.6007680, Perkin Elmer) at the density of 7 500 cells/well in 20µl. Cell are stored over night at 37°C, 5% CO<sub>2</sub> until used.

Compounds in 100% DMSO (0.315µl/well) were resuspended in 20µl MEM, 1% FBS, 3.4% DMSO. Compounds and andrographolide (10µM final concentration; Ref.365645-500MG,

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Aldrich)) as positive control, were dispensed on cell, 5µl/well, and then incubated for 3h at 37°C and 5% CO<sub>2</sub>. After incubation, Path hunter reagents were dispensed on cells (12µl/well, Ref.93-0001, DiscoverX) and incubated for 60 min at room temperature in the dark.

Then, luminescence signal was measured using multimodal reader (Pherastar, BMG Labtech).

- 5 Data were normalized between 1% DMSO (basal signal) and 10µM andrographolide (positive signal) and analyzed using Activity Base software.

| EXAMPLE | CELLULAR U2OS<br>EC <sub>50</sub> (nM) |
|---------|----------------------------------------|
| 1a      | 10,1                                   |
| 1b      | 735                                    |
| 2       | 830                                    |
| 3a      | 79,5                                   |
| 3b      | 10,6                                   |
| 4       | 3470                                   |
| 5       | 1810                                   |
| 6       | 1330                                   |
| 7a      | 23                                     |
| 7b      | 290                                    |
| 8a      | 986                                    |
| 8b      | 516                                    |
| 9a      | 48,2                                   |
| 9b      | 845                                    |
| 10a     | 58,1                                   |
| 10b     | 369                                    |
| 11a     | 109                                    |
| 11b     | 13,1                                   |
| 12a     | 3160                                   |
| 12b     | >3160                                  |
| 13a     | 232                                    |
| 13b     | 26,7                                   |
| 14      | 582                                    |
| 15a     | 57,9                                   |

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| EXAMPLE | CELLULAR U2OS<br>EC50 (nM) |
|---------|----------------------------|
| 15b     | 381                        |
| 16a     | 871                        |
| 16b     | 108                        |
| 17a     | 1660                       |
| 17b     | 89                         |
| 18a     | 1140                       |
| 18b     | 91,3                       |
| 19a     | 73,6                       |
| 19b     | 2,76                       |
| 20a     | 1,99                       |
| 20b     | 131                        |
| 21a     | 10,9                       |
| 21b     | 166                        |
| 22a     | 17,2                       |
| 22b     | 111                        |
| 23a     | 3160                       |
| 23b     | 344                        |
| 24a     | 7,28                       |
| 24b     | 2,45                       |
| 24c     | 60                         |
| 24d     | 36,4                       |
| 25a     | 14                         |
| 25b     | 56,8                       |
| 26a     | 11,3                       |
| 26b     | 88,8                       |
| 27a     | 93,1                       |
| 27b     | 16,2                       |
| 28a     | 611                        |
| 28b     | 15,3                       |
| 28c     | >3160                      |
| 28d     | 879                        |
| 29a     | 440                        |
| 29b     | 68,4                       |

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| EXAMPLE | CELLULAR U2OS<br>EC50 (nM) |
|---------|----------------------------|
| 30a     | 555                        |
| 30b     | 2360                       |
| 31a     | 1430                       |
| 31b     | 27,4                       |
| 31c     | >3160                      |
| 31d     | 326                        |
| 32a     | 20                         |
| 32b     | 150                        |
| 33a     | 94,5                       |
| 33b     | 894                        |
| 34a     | 2,66                       |
| 34b     | 31,1                       |
| 35a     | >3160                      |
| 35b     | >3160                      |
| 36a     | 126                        |
| 36b     | 1260                       |
| 37a     | 1300                       |
| 37b     | >3160                      |
| 38a     | 2080                       |
| 38b     | >3160                      |
| 39a     | 14,2                       |
| 39b     | 79,5                       |
| 40a     | 9,72                       |
| 40b     | 353                        |
| 41a     | 716                        |
| 41b     | >3160                      |
| 42      | 21,4                       |
| 43      | 570                        |
| 44      | 292                        |
| 45a     | 11,8                       |
| 45b     | 144                        |
| 46a     | 228                        |
| 46b     | 792                        |

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| EXAMPLE | CELLULAR U2OS<br>EC50 (nM) |
|---------|----------------------------|
| 47      | 288                        |
| 48      | 198                        |
| 49      | 1620                       |
| 50      | 139                        |
| 51      | 103                        |
| 52      | 180                        |
| 53a     | 369                        |
| 53b     | 899                        |
| 54a     | 1290                       |
| 54b     | 2270                       |
| 55a     | 183                        |
| 55b     | 15,8                       |
| 56      | 214                        |
| 57a     | 496                        |
| 57b     | 2820                       |
| 58a     | 90,4                       |
| 58b     | 427                        |
| 59a     | 311                        |
| 59b     | 1760                       |
| 60a     | 265                        |
| 60b     | >3160                      |
| 61a     | 717                        |
| 61b     | >3160                      |
| 62a     | 177                        |
| 62b     | >3160                      |
| 63a     | 57,1                       |
| 63b     | 1220                       |
| 64a     | 24                         |
| 64b     | 231                        |
| 65      | 699                        |
| 66a     | 3,44                       |
| 66b     | 17,9                       |
| 67a     | 554                        |

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| EXAMPLE | CELLULAR U2OS<br>EC50 (nM) |
|---------|----------------------------|
| 67b     | >3160                      |
| 68      | 38,3                       |
| 69      | >3160                      |
| 70a     | 306                        |
| 70b     | >3160                      |
| 71a     | 42                         |
| 71b     | 570                        |
| 72a     | >3160                      |
| 72b     | >3160                      |
| 73a     | 63,4                       |
| 73b     | 707                        |
| 74a     | 6,11                       |
| 74b     | 756                        |
| 75      | 59,6                       |
| 76a     | 7,5                        |
| 76b     | 26,2                       |
| 77a     | 1750                       |
| 77b     | >3160                      |
| 78a     | 69                         |
| 78b     | 873                        |
| 79a     | 1120                       |
| 79b     | 296                        |
| 80a     | 596                        |
| 80b     | 2700                       |
| 81a     | 275                        |
| 81b     | >3160                      |
| 82a     | 635                        |
| 82b     | >3160                      |

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**EXAMPLE 85 : Surface Plasmon Resonance**

Binding assay to Kelch domain of KEAP1 was performed by Surface Plasmon Resonance (SPR) on a Biacore T200 (GE Healthcare) at 25°C using CM5 chip. His-Thromb-KEAP1(A321-C624) acquired from Novalix (batch PU-P01) was immobilized covalently by amine coupling using standard wizard protocol, at a concentration of 20 µg/mL in sodium acetate pH 5.5. The ligand was captured until 1250 RU was reached. Amine blank is used as the reference flow cell. Binding of analyte to the ligand was monitored in real time with associations of 180 seconds and a dissociation of 720 seconds. Association ( $k_a$ ) and dissociation ( $k_d$ ) rates were fitted with a simple 1:1 kinetic interaction model using Biacore T200 Evaluation Software (GE Healthcare). The equilibrium constant ( $K_D=k_d/k_a$ ) was calculated from these fitted parameters. In the experiment, a half-log dilution of the compound was injected over KEAP1 in Single Cycle Kinetics (SCK) with 5 increasing concentrations of 0.316, 1, 3.16, 10 and 31.6 nM per cycle. The Biacore binding assay was performed with a flowrate of 50µL/min using a running buffer of 10 mM HEPES (pH 7.4), 150 mM NaCl, 3mM EDTA, 1 mM TCEP, 0.05% P20, 5% DMSO. Double subtraction was used by subtracting both reference flow cell and previous blank cycle (with running buffer). Solvent correction was applied to correct DMSO bulk effect.

| EXAMPLE | Keap1 (A321-C624) (h)<br>direct/SPR (KD) [M] |
|---------|----------------------------------------------|
| 1a      | 1,8100E-10                                   |
| 1b      | 3,9700E-09                                   |
| 2       | 3,5200E-08                                   |
| 3a      | 7,6400E-09                                   |
| 3b      | 1,0500E-09                                   |
| 4       | 2,5500E-07                                   |
| 5       | 1,3100E-07                                   |
| 6       | 3,3700E-08                                   |
| 7a      | 1,0700E-09                                   |

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| <b>EXAMPLE</b> | <b>Keap1 (A321-C624) (h)<br/>direct/SPR (KD) [M]</b> |
|----------------|------------------------------------------------------|
| <b>7b</b>      | 4,8600E-09                                           |
| <b>8a</b>      | 6,2200E-08                                           |
| <b>8b</b>      | 1,2400E-08                                           |
| <b>9a</b>      | 2,1200E-09                                           |
| <b>9b</b>      | 9,9900E-09                                           |
| <b>10a</b>     | 3,5400E-09                                           |
| <b>10b</b>     | 1,5100E-08                                           |
| <b>11a</b>     | 2,4200E-09                                           |
| <b>11b</b>     | 7,7800E-10                                           |
| <b>12a</b>     | 3,0700E-06                                           |
| <b>12b</b>     | 2,9200E-06                                           |
| <b>13a</b>     | 1,6200E-08                                           |
| <b>13b</b>     | 4,1500E-09                                           |
| <b>14</b>      | 1,4200E-08                                           |
| <b>15a</b>     | 1,9200E-09                                           |
| <b>15b</b>     | 4,4100E-09                                           |
| <b>16a</b>     | 4,0300E-09                                           |
| <b>16b</b>     | 1,7300E-09                                           |
| <b>17a</b>     | 2,5700E-08                                           |
| <b>17b</b>     | 5,5500E-09                                           |
| <b>18a</b>     | 3,6700E-09                                           |
| <b>18b</b>     | 1,0100E-09                                           |
| <b>19a</b>     | 1,3400E-09                                           |
| <b>19b</b>     | 6,4600E-10                                           |
| <b>20a</b>     | 5,4900E-10                                           |
| <b>20b</b>     | 2,3000E-09                                           |
| <b>21a</b>     | 2,5500E-09                                           |



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| <b>EXAMPLE</b> | <b>Keap1 (A321-C624) (h)<br/>direct/SPR (KD) [M]</b> |
|----------------|------------------------------------------------------|
| <b>21b</b>     | 2,0800E-08                                           |
| <b>22a</b>     | 6,3100E-10                                           |
| <b>22b</b>     | 2,1100E-09                                           |
| <b>23a</b>     | 5,0500E-08                                           |
| <b>23b</b>     | 8,8000E-09                                           |
| <b>24a</b>     | 1,1000E-09                                           |
| <b>24b</b>     | 1,2300E-09                                           |
| <b>24c</b>     | 5,0000E-09                                           |
| <b>24d</b>     | 4,3200E-09                                           |
| <b>25a</b>     | 5,6200E-10                                           |
| <b>25b</b>     | 1,1600E-09                                           |
| <b>26a</b>     | 3,4000E-09                                           |
| <b>26b</b>     | 1,2200E-08                                           |
| <b>27a</b>     | 1,4200E-08                                           |
| <b>27b</b>     | 3,5600E-09                                           |
| <b>28a</b>     | 2,3400E-08                                           |
| <b>28b</b>     | 3,2500E-09                                           |
| <b>32a</b>     | 6,4500E-10                                           |
| <b>32b</b>     | 2,0200E-09                                           |
| <b>33a</b>     | 4,5500E-09                                           |
| <b>33b</b>     | 9,2900E-09                                           |
| <b>34a</b>     | 4,9000E-10                                           |
| <b>34b</b>     | 1,8500E-09                                           |
| <b>35a</b>     | 3,3600E-05                                           |
| <b>35b</b>     | 7,4500E-06                                           |
| <b>36a</b>     | 9,0200E-09                                           |
| <b>36b</b>     | 3,2500E-08                                           |

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| <b>EXAMPLE</b> | <b>Keap1 (A321-C624) (h)<br/>direct/SPR (KD) [M]</b> |
|----------------|------------------------------------------------------|
| <b>37a</b>     | 7,5100E-08                                           |
| <b>37b</b>     | 5,2900E-07                                           |
| <b>38b</b>     | 6,0400E-07                                           |
| <b>39a</b>     | 1,3700E-10                                           |
| <b>39b</b>     | 6,8500E-10                                           |
| <b>40a</b>     | 5,5100E-09                                           |
| <b>40b</b>     | 2,2300E-08                                           |
| <b>42</b>      | 1,5700E-09                                           |
| <b>43</b>      | 2,9200E-09                                           |
| <b>44</b>      | 1,4600E-10                                           |
| <b>45a</b>     | 5,9400E-10                                           |
| <b>45b</b>     | 2,3500E-09                                           |
| <b>50</b>      | 5,9700E-09                                           |
| <b>51</b>      | 2,0300E-09                                           |
| <b>52</b>      | 8,8600E-09                                           |
| <b>53a</b>     | 4,7700E-08                                           |
| <b>53b</b>     | 1,7600E-07                                           |
| <b>54a</b>     | 9,0500E-08                                           |
| <b>54b</b>     | 3,9100E-07                                           |
| <b>55a</b>     | 2,0000E-09                                           |
| <b>55b</b>     | 2,5000E-09                                           |
| <b>56</b>      | 1,2600E-08                                           |
| <b>57a</b>     | 5,8900E-08                                           |
| <b>57b</b>     | 4,9800E-07                                           |
| <b>58a</b>     | 4,6600E-09                                           |
| <b>58b</b>     | 1,2500E-08                                           |
| <b>59a</b>     | 5,0700E-09                                           |

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| EXAMPLE | Keap1 (A321-C624) (h)<br>direct/SPR (KD) [M] |
|---------|----------------------------------------------|
| 62a     | 3,0000E-09                                   |
| 63a     | 4,3900E-09                                   |
| 64a     | 1,9500E-10                                   |
| 66a     | 6,7800E-10                                   |
| 66b     | 8,3300E-10                                   |
| 68      | 8,9600E-09                                   |
| 71a     | 1,9300E-08                                   |
| 72a     | 2,3600E-08                                   |
| 72b     | 7,3000E-07                                   |
| 73a     | 6,2300E-09                                   |
| 73b     | 1,7600E-08                                   |

**EXAMPLE 86 : Target engagement study**

Target engagement was assessed in fed db/db mice (8 week-old, Janvier Labs). Compounds  
 5 were orally administered at the doses of 30 and/or 100 mg/kg (10 mL/kg in HEC 1%) or  
 vehicle. After mouse anesthesia, blood and liver samples were taken 4, 6 and 24 hours after  
 administration. Compound concentration was determined both in plasma and liver at each  
 time point. Activation of NRF2 by compounds was measured by the increase of Nqo1 gene  
 expression in liver of treated mice versus controlled mice.

10

**EXAMPLE 87 : Oral Glucose Tolerance Test study (OGTT)**

The efficacy of compounds on glucose tolerance was assessed in ob/ob mice (10-wk,  
 Janvier Labs). Compounds were administered at 30 and/or 100 mg/kg (10 mL/kg in HEC  
 15 1%) for 10 days. Immediately after the last administration, mice were fasted for 4 hours.  
 An oral glucose tolerance test was then performed with the measurement of blood glucose  
 and plasma insulin levels before and at different time points after glucose administration

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(1.5 g/kg, 10 mL/kg in water). Mice were then provided with food ad libitum. On the day after OGTT, mice were sacrificed and the liver taken. Target engagement was then confirmed by measuring the increase of Nqo1 gene expression in the liver of compound-treated mice versus controlled mice.

5

**EXAMPLE 88 : Efficacy study in NASH using MCD model**

The efficacy of compounds in NASH was addressed using the murine model of NASH induced by Methionine and Choline Deficient (MCD) diet. Treatment with compound and  
10 NASH induction by the diet started concomitantly. Mice were placed under MCD diet and treatment with compounds started immediately for 14 days. Mice were weighed and orally administered with compounds (10 mL/kg in HEC 1%). After 14 days of treatment and diet, 4hr-fasted mice were euthanized. Blood samples were obtained for hepatic enzyme determination (Alanine aminotransferase (ALT) and Aspartate aminotransferase (AST)).  
15 Liver were taken for NASH analysis and target engagement measurement. Hepatic triglyceride content was quantified. NASH was determined by the measurement of steatosis, inflammation and by the quantification of the NAFLD Activity Score (NAS). Target engagement was then confirmed by measuring the increase of Nqo1 gene expression in the liver of compound-treated mice versus controlled mice.

20

**EXAMPLE 89 : Efficacy study in ADPKD**

In order to assess the efficacy of Nrf2 activators, we use conditional and inducible *Pkd1* gene deficient mice as initially described (Lantinga-van Leeuwen et al, Hum Mol Genet. 2007,  
25 16(24), 3188-96). Upon tamoxifen injection to 10d-old mice (p10), *Pkd1* gene is specifically deleted in renal epithelium. This leads to quick progression of cyst formation in the distal segment of the nephron. Mice then receive either tested molecule (3 to 30 mg/kg/d) or vehicle (HydroxyEthylCellulose 1%) for 2 to 3 weeks by gavage. At the end of the treatment, all the mice are sacrificed and both plasma and kidneys are collected. Plasma samples are used to  
30 monitor drug exposure at the end of the study. Efficacy is determined by quantifying the impact

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of the treatment on kidney size, kidney weight, kidney weight to body weight ratio, cystic index (determined by histological analysis) and urea volume as a proxy of kidney function as previously described (Lu et al., Sci. Transl. Med. 12, eaba3613 (2020) 29 July 2020 “Activation of NRF2 ameliorates oxidative stress and cystogenesis in autosomal dominant polycystic kidney disease”). Nrf2 target engagement can be monitored either by measuring Nrf2 target gene activation such as Nqo1 or by directly quantifying Reactive Oxygen Species (ROS) in the kidney using standard assay kits.

#### **EXAMPLE 90 : Pharmaceutical composition**

10

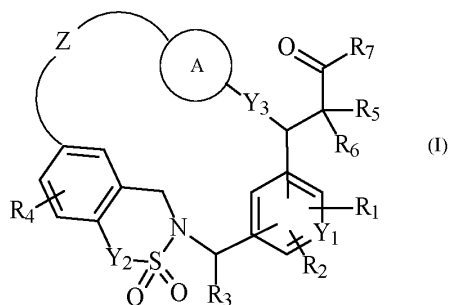
Formulation for the preparation of 1000 tablets each containing 10 mg:

|    |                                                |
|----|------------------------------------------------|
| 10 | Compound of one of Examples 1 to 82 ..... 10 g |
|    | Hydroxypropylcellulose..... 2 g                |
|    | Wheat starch..... 10 g                         |
| 15 | Lactose .....100 g                             |
|    | Magnesium stearate.....3 g                     |
|    | Talc .....3 g                                  |

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## CLAIMS

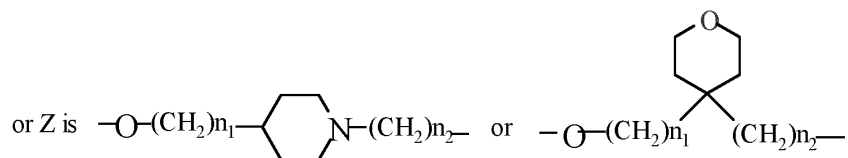
1. A compound of formula (I) :



5

wherein

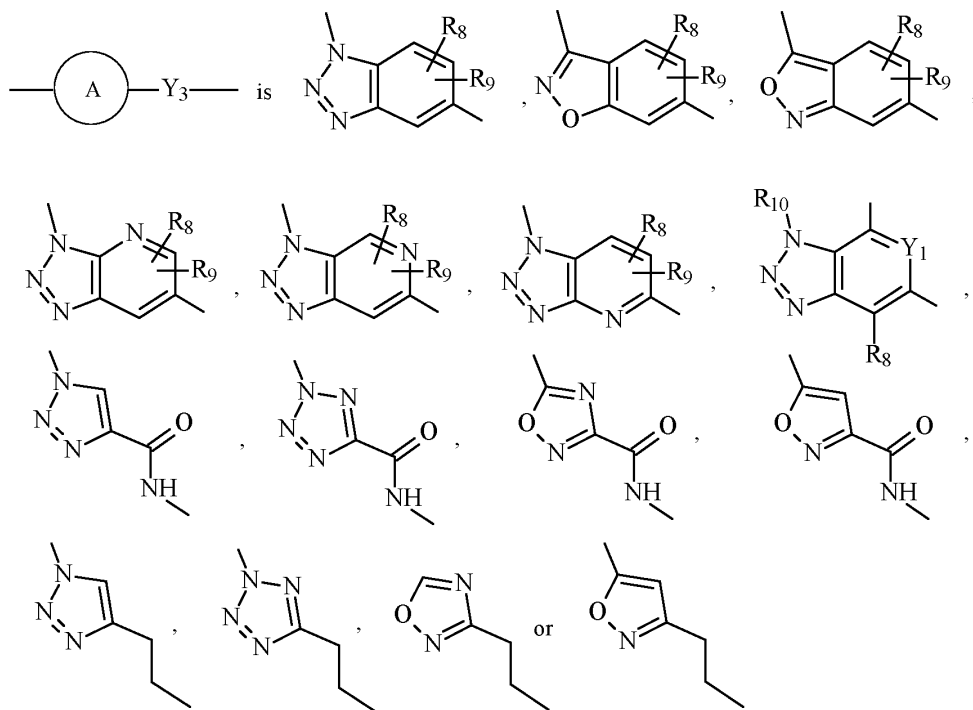
Z is -O-(CH<sub>2</sub>)<sub>n1</sub>-, -O-(CH<sub>2</sub>)<sub>n1</sub>-O-(CH<sub>2</sub>)<sub>n2</sub>-, -O-(CH<sub>2</sub>)<sub>n1</sub>-S-(CH<sub>2</sub>)<sub>n2</sub>-, O-(CH<sub>2</sub>)<sub>n1</sub>-S(O)-(CH<sub>2</sub>)<sub>n2</sub>-, O-(CH<sub>2</sub>)<sub>n1</sub>-S(O<sub>2</sub>)-(CH<sub>2</sub>)<sub>n2</sub>-, -O-(CH<sub>2</sub>)<sub>n1</sub>-NR-(CH<sub>2</sub>)<sub>n2</sub>-, -O-(CH<sub>2</sub>)<sub>n1</sub>-CHR'-(CH<sub>2</sub>)<sub>n2</sub>-, -NR-(CH<sub>2</sub>)<sub>n1</sub>-, -NR-(CO)-(CH<sub>2</sub>)<sub>n1</sub>-, -O-(CH<sub>2</sub>)<sub>n1</sub>-Ar-(CH<sub>2</sub>)<sub>n2</sub>-, -O-(CH<sub>2</sub>)<sub>n1</sub>-Ar-O-(CH<sub>2</sub>)<sub>n2</sub>-, -O-(CH<sub>2</sub>)<sub>n1</sub>-Ar-S-(CH<sub>2</sub>)<sub>n2</sub>-, -O-(CH<sub>2</sub>)<sub>n1</sub>-Ar-S(O)-(CH<sub>2</sub>)<sub>n2</sub>-, -O-(CH<sub>2</sub>)<sub>n1</sub>-Ar-S(O<sub>2</sub>)-(CH<sub>2</sub>)<sub>n2</sub>-, -O-(CH<sub>2</sub>)<sub>n1</sub>-Ar-CHR'-(CH<sub>2</sub>)<sub>n2</sub>-, -O-(CH<sub>2</sub>)<sub>n1</sub>-Ar-CH=CH-, O-Ar-NR-(CH<sub>2</sub>)<sub>n1</sub>-, -(CH<sub>2</sub>)<sub>n1</sub>-NR-(CO)-(CH<sub>2</sub>)<sub>n2</sub>-



$Y_1$  is C or N,

$Y_2$  is O or NR',

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Ar is an optionally substituted aryl or heteroaryl group,

5 R is a hydrogen atom, a linear or branched C<sub>1</sub>-C<sub>3</sub> alkyl group or an optionally substituted aryl group,

R' is a hydrogen atom or a group selected from hydroxyl, optionally substituted aryl and linear or branched C<sub>1</sub>-C<sub>3</sub> alkyl optionally substituted by alkoxy or by one to three halogen atoms,

n<sub>1</sub>, n<sub>2</sub> is an integer from 1 to 6,

10 R<sub>1</sub>, R<sub>2</sub>, R<sub>4</sub>, R<sub>8</sub>, R<sub>9</sub>, R<sub>10</sub>, identical or different, are each a hydrogen atom or a group selected from halo, cyano, linear or branched C<sub>1</sub>-C<sub>3</sub> alkyl optionally substituted by one to three halogen atoms, linear or branched C<sub>1</sub>-C<sub>3</sub> alkoxy or optionally substituted aryl,

R<sub>3</sub> is hydrogen or a linear or branched C<sub>1</sub>-C<sub>3</sub> alkyl group optionally substituted by one to three halogen atoms,

or R<sub>2</sub> and R<sub>3</sub> together form a ring with the atoms bearing them,

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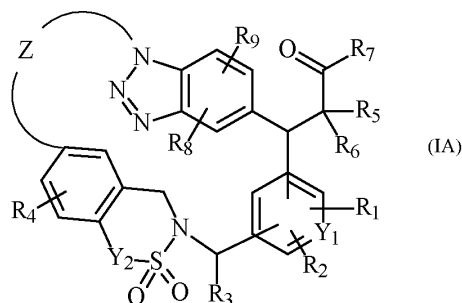
R<sub>5</sub>, R<sub>6</sub>, identical or different, are each a hydrogen, deuterium or halogen atom or a linear or branched C<sub>1</sub>-C<sub>3</sub> alkyl group,

R<sub>7</sub> is a group selected from hydroxyl and NHR'<sub>7</sub>,

wherein R'<sub>7</sub> is a linear or branched C<sub>1</sub>-C<sub>6</sub> alkyl group or an optionally substituted aryl or heteroaryl group,

its optical isomers, and addition salts thereof with a pharmaceutically acceptable base.

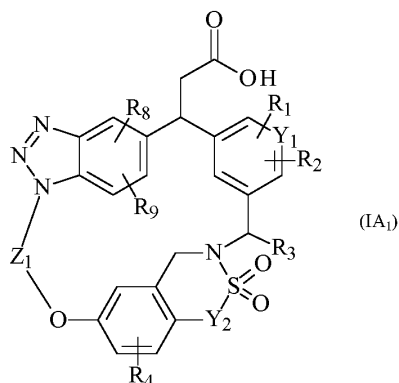
2. A compound according to claim 1 of formula (IA) :



wherein Z, Y<sub>1</sub>, Y<sub>2</sub>, R<sub>1</sub> to R<sub>9</sub> are as defined in claim 1,

its optical isomers, and addition salts thereof with a pharmaceutically acceptable base.

3. A compound according to claim 2 of formula (IA<sub>1</sub>) :



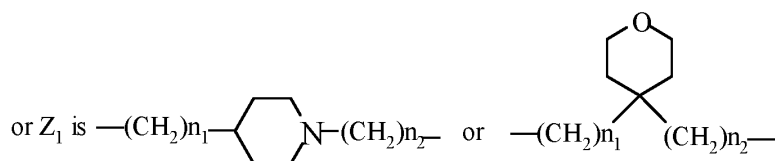
wherein R<sub>1</sub>-R<sub>4</sub>, R<sub>8</sub>-R<sub>9</sub>, Y<sub>1</sub>, Y<sub>2</sub> are as defined in claim 1, and Z<sub>1</sub> is a group selected from



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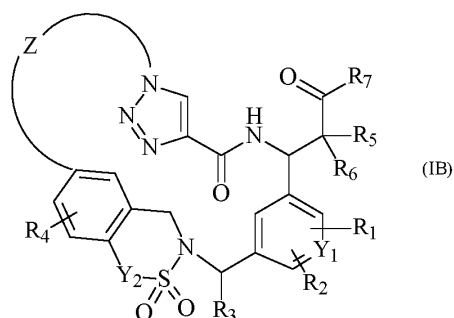
$-(CH_2)_{n_1}, -(CH_2)_{n_1}-O-(CH_2)_{n_2}, -(CH_2)_{n_1}-S-(CH_2)_{n_2}, -(CH_2)_{n_1}-NR-(CH_2)_{n_2}, -(CH_2)_{n_1}-$   
 $CHR'-(CH_2)_{n_2}, -(CH_2)_{n_1}-Ar_1-(CH_2)_{n_2}, -(CH_2)_{n_1}-Ar_1-O-(CH_2)_{n_2}, -(CH_2)_{n_1}-Ar_1-S-$   
 $(CH_2)_{n_2}, -(CH_2)_{n_1}-Ar_1-CHR'-(CH_2)_{n_2}, -Ar_1-NR-(CH_2)_{n_1},$

5



its optical isomers, and addition salts thereof with a pharmaceutically acceptable base.

4. A compound according to claim 1 of formula (IB) :



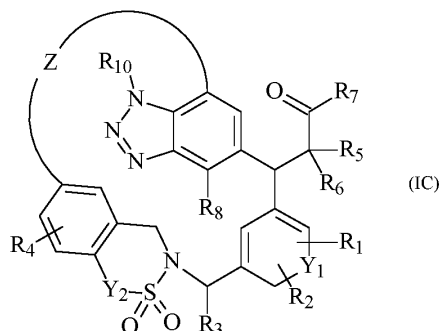
10

wherein Z, Y<sub>1</sub>, Y<sub>2</sub>, R<sub>1</sub> to R<sub>7</sub> are as defined in claim 1,

its optical isomers, and addition salts thereof with a pharmaceutically acceptable base.

5. A compound according to claim 1 of formula (IC) :

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wherein Z, Y<sub>1</sub>, Y<sub>2</sub>, R<sub>1</sub> to R<sub>8</sub> and R<sub>10</sub> are as defined in claim 1,

its optical isomers, and addition salts thereof with a pharmaceutically acceptable base.

6. A compound of formula (I) according to any one of claims 1, 2, 4 or 5, wherein Z is -O-  
 5 (CH<sub>2</sub>)<sub>n1</sub>-, -O-(CH<sub>2</sub>)<sub>n1</sub>-O-(CH<sub>2</sub>)<sub>n2</sub> or -O-(CH<sub>2</sub>)<sub>n1</sub>-S-(CH<sub>2</sub>)<sub>n2</sub>.

7. A compound of formula (I) according to any one of claims 1 to 6, wherein Y<sub>1</sub> is C.

8. A compound of formula (I) according to any one of claims 1 to 7, wherein Y<sub>2</sub> is O or NCH<sub>3</sub>.

10

9. A compound of formula (I) according to claim 1, which is selected from :

[4,32-dimethyl-28,28-dioxo-22,27-dioxa-28λ<sup>6</sup>-thia-1,14,15,16-tetraazahexacyclo  
 [21.5.3.1<sup>3,7</sup>.1<sup>9,13</sup>.0<sup>12,16</sup>.0<sup>26,30</sup>]tritiaconta-3(33),4,6,9(32),10,12,14,23,25,30-decaen-8-  
 yl]acetic acid, its optical isomers, and addition salts thereof with a pharmaceutically  
 15 acceptable base,

[2,4,31-trimethyl-27,27-dioxo-21,26-dioxa-27λ<sup>6</sup>-thia-1,14,15,16-tetraazahexacyclo  
 [20.5.3.1<sup>3,7</sup>.1<sup>9,13</sup>.0<sup>12,16</sup>.0<sup>25,29</sup>]dotriaconta-3(32),4,6,9(31),10,12,14,22,24,29-decaen-8-  
 yl]acetic acid, its optical isomers, and addition salts thereof with a pharmaceutically  
 acceptable base,

20

[4,31-dimethyl-27,27-dioxo-21,26-dioxa-27λ<sup>6</sup>-thia-1,14,15,16-tetraazahexacyclo  
 [20.5.3.1<sup>3,7</sup>.1<sup>9,13</sup>.0<sup>12,16</sup>.0<sup>25,29</sup>]dotriaconta-3(32),4,6,9(31),10,12,14,22,24,29-decaen-8-  
 yl]acetic acid, its optical isomers, and addition salts thereof with a pharmaceutically  
 acceptable base,

25

[4-chloro-31-methyl-27,27-dioxo-21,26-dioxa-27λ<sup>6</sup>-thia-1,14,15,16-tetraazahexacyclo  
 [20.5.3.1<sup>3,7</sup>.1<sup>9,13</sup>.0<sup>12,16</sup>.0<sup>25,29</sup>]dotriaconta-3(32),4,6,9(31),10,12,14,22,24,29-decaen-8-

-383-

yl]acetic acid, its optical isomers, and addition salts thereof with a pharmaceutically acceptable base,

5 [4-methoxy-31-methyl-27,27-dioxo-21,26-dioxa-27 $\lambda^6$ -thia-1,14,15,16-tetraazahexacyclo  
[20.5.3.1<sup>3,7</sup>.1<sup>9,13</sup>.0<sup>12,16</sup>.0<sup>25,29</sup>]dotriaconta-3(32),4,6,9(31),10,12,14,22,24,29-decaen-8-  
yl]acetic acid, its optical isomers, and addition salts thereof with a pharmaceutically  
acceptable base,

10 [4,33-dimethyl-29,29-dioxo-23,28-dioxa-29 $\lambda^6$ -thia-1,14,15,16-tetraazahexacyclo  
[22.5.3.1<sup>3,7</sup>.1<sup>9,13</sup>.0<sup>12,16</sup>.0<sup>27,31</sup>]tetratriaconta-3(34),4,6,9(33),10,12,14,24,26,31-decaen-8-  
yl]acetic acid, its optical isomers, and addition salts thereof with a pharmaceutically  
acceptable base,

[2,4,32-trimethyl-28,28-dioxo-19,22,27-trioxa-28 $\lambda^6$ -thia-1,14,15,16-tetraazahexacyclo  
[21.5.3.1<sup>3,7</sup>.1<sup>9,13</sup>.0<sup>12,16</sup>.0<sup>26,30</sup>]tritriaconta-3(33),4,6,9(32),10,12,14,23,25,30-decaen-8-  
yl]acetic acid, its optical isomers, and addition salts thereof with a pharmaceutically  
acceptable base,

15 [2,4,33-trimethyl-29,29-dioxo-23,28-dioxa-29 $\lambda^6$ -thia-1,14,15,16-  
tetraazahexacyclo[22.5.3.1<sup>3,7</sup>.1<sup>9,13</sup>.0<sup>12,16</sup>.0<sup>27,31</sup>]tetratriaconta-  
3(34),4,6,9(33),10,12,14,24,26,31-decaen-8-yl]acetic acid, its optical isomers, and addition  
salts thereof with a pharmaceutically acceptable base,

20 [23-chloro-4,31-dimethyl-27,27-dioxo-21,26-dioxa-27 $\lambda^6$ -thia-1,14,15,16-tetraazahexacyclo  
[20.5.3.1<sup>3,7</sup>.1<sup>9,13</sup>.0<sup>12,16</sup>.0<sup>25,29</sup>]dotriaconta-3(32),4,6,9(31),10,12,14,22,24,29-decaen-8-  
yl]acetic acid, its optical isomers, and addition salts thereof with a pharmaceutically  
acceptable base,

25 [23-methoxy-4,31-dimethyl-27,27-dioxo-21,26-dioxa-27 $\lambda^6$ -thia-1,14,15,16-  
tetraazahexacyclo[20.5.3.1<sup>3,7</sup>.1<sup>9,13</sup>.0<sup>12,16</sup>.0<sup>25,29</sup>]dotriaconta-  
3(32),4,6,9(31),10,12,14,22,24,29-decaen-8-yl]acetic acid, its optical isomers, and addition  
salts thereof with a pharmaceutically acceptable base,

30 [23-fluoro-4,31-dimethyl-27,27-dioxo-21,26-dioxa-27 $\lambda^6$ -thia-1,14,15,16-tetraazahexacyclo  
[20.5.3.1<sup>3,7</sup>.1<sup>9,13</sup>.0<sup>12,16</sup>.0<sup>25,29</sup>]dotriaconta-3(32),4,6,9(31),10,12,14,22,24,29-decaen-8-  
yl]acetic acid, its optical isomers, and addition salts thereof with a pharmaceutically  
acceptable base,

[4,26,31-trimethyl-27,27-dioxo-21-oxa-27 $\lambda^6$ -thia-1,14,15,16,26-pentaazahexacyclo  
[20.5.3.1<sup>3,7</sup>.1<sup>9,13</sup>.0<sup>12,16</sup>.0<sup>25,29</sup>]dotriaconta-3(32),4,6,9(31),10,12,14,22,24,29-decaen-8-  
yl]acetic acid, its optical isomers, and addition salts thereof with a pharmaceutically  
acceptable base,

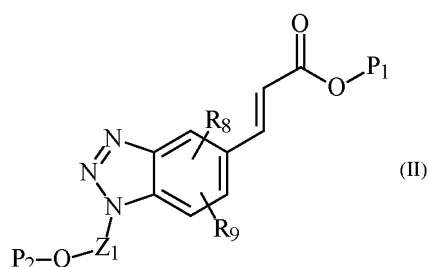
-384-

[4,32-dimethyl-28,28-dioxo-22,27-dioxa-19,28 $\lambda^6$ -dithia-1,14,15,16-tetraazahexacyclo  
[21.5.3.1<sup>3,7</sup>.1<sup>9,13</sup>.0<sup>12,16</sup>.0<sup>26,30</sup>]tritriaconta-3(33),4,6,9(32),10,12,14,23,25,30-decaen-8-  
yl]acetic acid, its optical isomers, and addition salts thereof with a pharmaceutically  
acceptable base,

- 5 [30-chloro-4,31-dimethyl-27,27-dioxo-21,26-dioxa-27 $\lambda^6$ -thia-1,14,15,16-tetraazahexacyclo  
[20.5.3.1<sup>3,7</sup>.1<sup>9,13</sup>.0<sup>12,16</sup>.0<sup>25,29</sup>]dotriaconta-3(32),4,6,9(31),10,12,14,22,24,29-decaen-8-  
yl]acetic acid, its optical isomers, and addition salts thereof with a pharmaceutically  
acceptable base,

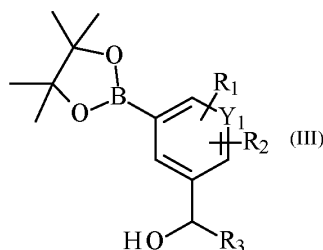
- 10 [4,32-dimethyl-28,28-dioxo-19,22,27-trioxa-28 $\lambda^6$ -thia-1,14,15,16-tetraazahexacyclo  
[21.5.3.1<sup>3,7</sup>.1<sup>9,13</sup>.0<sup>12,16</sup>.0<sup>26,30</sup>]tritriaconta-3(33),4,6,9(32),10,12,14,23,25,30-decaen-8-  
yl]acetic acid, its optical isomers, and addition salts thereof with a pharmaceutically  
acceptable base.

- 15 **10.** A process for the preparation of a compound of formula (IA<sub>1</sub>) according to claim 3, starting  
from a compound of formula (II) :



wherein P<sub>1</sub> is a protecting group of the acid function, and P<sub>2</sub> is a protecting group of the  
alcohol function,

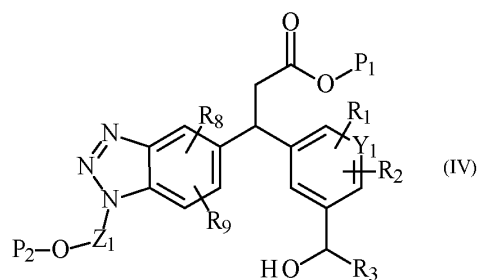
which is reacted with a compound of formula (III) :



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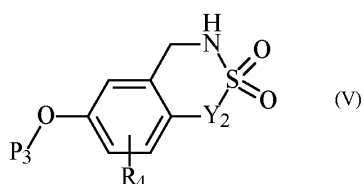
wherein  $R_1$ - $R_3$  and  $Y_1$  are as defined in claim 1,

to give a compound of formula (IV) :



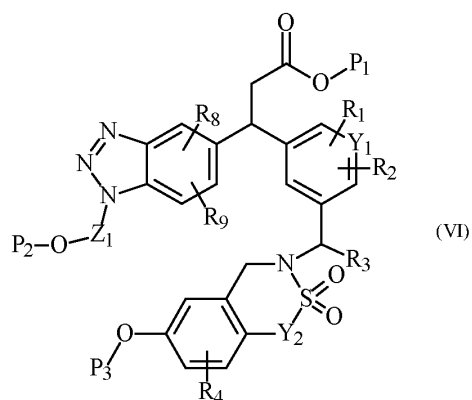
wherein  $R_1$ - $R_3$ ,  $R_8$ - $R_9$ ,  $Y_1$ ,  $Z_1$  and  $P_1$ - $P_2$  are as defined before,

5 which is reacted with a compound of formula (V) :



wherein  $R_4$  and  $Y_2$  are as defined in claim 1, and  $P_3$  is a protecting group of the alcohol function,

to give a compound of formula (VI) :

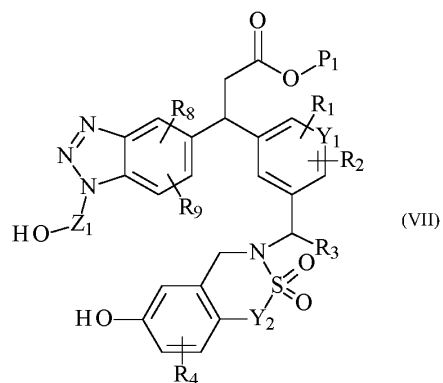


10

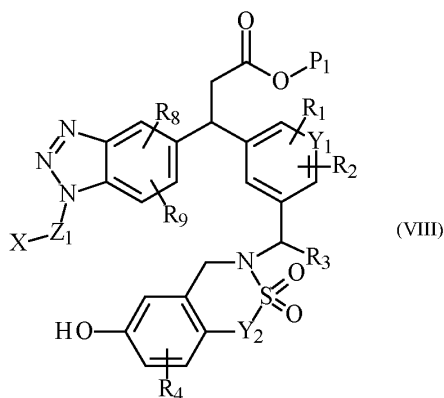
wherein  $R_1$ - $R_4$ ,  $R_8$ - $R_9$ ,  $Y_1$ ,  $Y_2$ ,  $Z_1$  and  $P_1$ - $P_3$  are as defined before,

which is deprotected to give a compound of formula (VII) :

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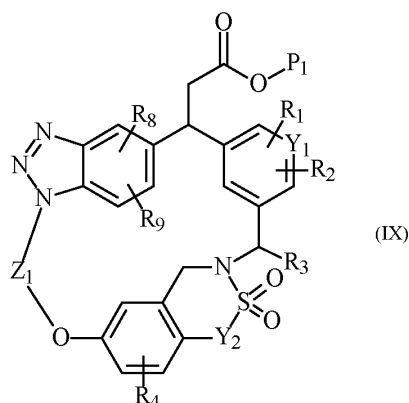


wherein R<sub>1</sub>-R<sub>4</sub>, R<sub>8</sub>-R<sub>9</sub>, Y<sub>1</sub>, Y<sub>2</sub>, Z<sub>1</sub> and P<sub>1</sub> are as defined before,  
which is halogenated to give a compound of formula (VIII) :



- 5 wherein R<sub>1</sub>-R<sub>4</sub>, R<sub>8</sub>-R<sub>9</sub>, Y<sub>1</sub>, Y<sub>2</sub>, Z<sub>1</sub> and P<sub>1</sub> are as defined before, and X is a halogen atom,  
which is reacted with a base to give a compound of formula (IX) :

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which is deprotected by reaction of a base to give a compound of formula (IA<sub>1</sub>), the stereoisomers thereof are separated, if desired, using chiral separation techniques.

- 5     **11.** A pharmaceutical composition comprising a compound of formula (I) according to any  
one of claims 1 to 9, in combination with one or more inert, non-toxic,  
pharmaceutically acceptable excipients or carriers.
- 10     **12.** A pharmaceutical composition according to claim 11, characterised in that it further  
comprises one or more further active ingredients.
- 15     **13.** A compound according to any one of claims 1 to 9 for use as an Nrf2 activator.
- 14.** A compound according to any one of claims 1 to 9 for use in the treatment of diseases  
that are linked to increased oxidative stress and inflammation, impaired redox  
potential, impaired detoxification or deregulated metabolism.
- 15.** A compound according to any one of claims 1 to 9 for use in the treatment of type II  
diabetes, non alcoholic steatohepatitis, Autosomal dominant polycystic kidney disease,  
Acute Kidney Injury, Alport Syndrome or Alström syndrome.