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Authors	Imre Gyűjtő, Márta Porcs-Makkay, Ernák Ferenc Várda, Gyöngyvér Pusztai, Gábor Tóth, Gyula Simig and Balázs Volk
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ORCID® iDs	Balázs Volk - https://orcid.org/0000-0002-2019-1874

Transformation of 2*H*-1,2,3-benzothiadiazine 1,1-dioxides variously substituted at the aromatic ring, *via* nucleophilic substitution and demethylation reactions

Imre Gyűjtő,[a,b] Márta Porcs-Makkay,[a] Ernák Ferenc Várda,[a] Gyöngyvér Pusztai,[a] Gábor Tóth,[a,b] Gyula Simig,[a] Balázs Volk[a,*]

[a] Directorate of Drug Substance Development, Egis Pharmaceuticals Plc., P.O. Box 100, H-1475 Budapest, Hungary

[b] Department of Inorganic and Analytical Chemistry, Budapest University of Technology and Economics, Szent Gellért tér 4, H-1111 Budapest, Hungary

* To whom correspondence should be addressed. Phone: +36 1 8035874, e-mail: volk.balazs@egis.hu

Abstract

2*H*-1,2,3-Benzothiadiazine 1,1-dioxides are a class of compounds of pharmacological interest. After earlier studies carried out at our laboratory on various transformations (alkylation, acylation, reduction) at the hetero ring, the present manuscript focuses on the transformation of substituents at the aromatic carbocycle, including nucleophilic substitution of chlorine atoms and demethylation of the methoxy group with amines. The new methods described here allow the introduction of versatile functional groups on the aromatic ring, making these compounds useful building blocks for organic and medicinal chemistry applications.

Keywords

2*H*-1,2,3-benzothiadiazine 1,1-dioxide, S_NAr, amination, demethylation, debenzylation, NMR

Introduction

In drug discovery, heterocyclic ring systems either demonstrate pharmacological effect themselves or can serve as core molecules to which pharmacophores can be attached. During our research aiming to identify new drug candidates with a potential central nervous system (CNS) activity, we applied this dual strategy in the development of 2*H*-1,2,3-benzothiadiazine 1,1-dioxides (BTDs, Fig. 1).[1]

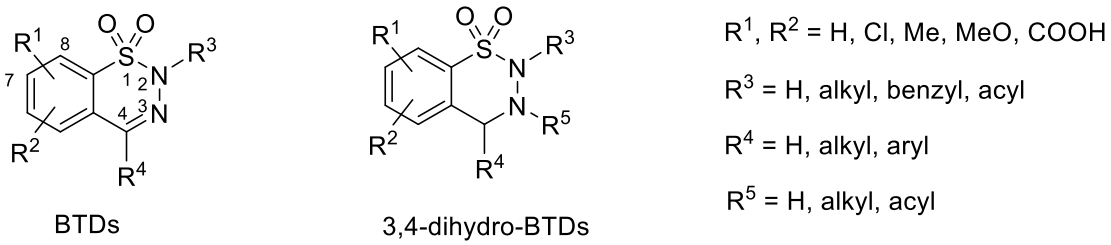


Figure 1. 2*H*-1,2,3-Benzothiadiazine 1,1-dioxide (BTD) derivatives

Earlier, we published the synthesis of 4-unsubstituted (Fig. 1, R^4=H),[2–4] 4-phenyl (R^4=Ph)[5] and 4-methyl (R^4=Me) derivatives[6] and their 3,4-dihydro counterparts, and targeted *N*(2)- and *N*(3)-alkylation[7,8] and acylation[9] reactions have also been elaborated. The *in vivo* anxiolytic effect of 4-unsubstituted BTDs[7] and *in vitro* positive AMPA modulator (PAM) activity of 4-aryl derivatives[5] was also studied. Moreover, we disclosed chlorine-lithium exchange at position 8 of the aromatic ring and subsequent introduction of electrophiles.[2,7] In this paper we present some possibilities for the further functionalization at position(s) 7 and/or 8 of the aromatic ring including chlorine-amine exchange reactions. Among the closest structural analogues of BTDs, examples are demonstrated for the reaction of amines with cyclic sulfonamides bearing an aromatic chlorine substituent either at the *ortho* or *meta* position (in respect to the sulfamoyl group) including 1,2,4-benzothiadiazine 1,1-dioxides[10] and 1,2-benzisothiazole 1,1-dioxides (Fig. 2).[11,12] In addition, cyclic sulfones also behave similarly.[13,14]

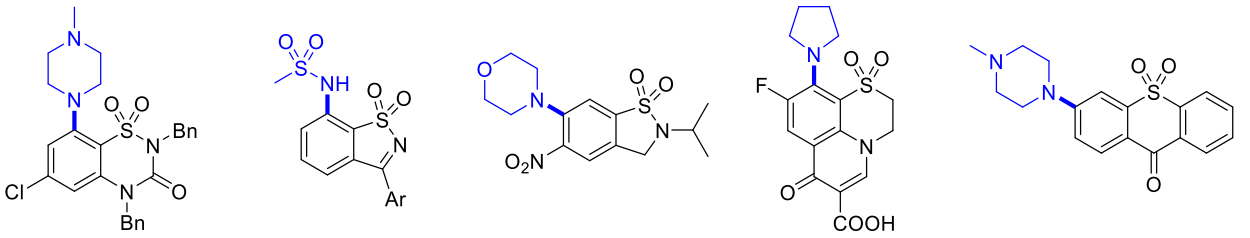
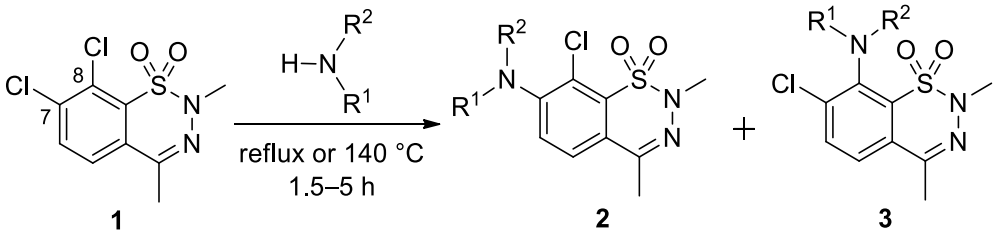


Figure 2. Literature examples for the amination of cyclic sulfonamides and sulfones (conditions of the chlorine-amine exchange are indicated below the structures)

Results and Discussion

7,8-Dichloro-2,4-dimethyl-BTD (**1**) was used as the model compound for the study of nucleophilic aromatic substitution reactions. It was reacted in neat with various amines (Table 1), including potential CNS pharmacophores (*N*-methylpiperazine, morpholine) or amines that are appropriate for further functionalization (2-aminoethanol). In most cases, a mixture of 7-amino-8-chloro (**2**) and 8-amino-7-chloro (**3**) derivatives was obtained after work-up, demonstrating that nucleophilic substitution took place both at positions 7 and 8. Secondary amines could be mainly introduced to the sterically less crowded position 7 (entries 1–4), whereas primary amines were more likely to attack at the electronically more favored position 8 (entries 5–8). No reaction took place with the bulky diisopropylamine (entry 9) or with aniline as an aromatic amine (entry 10). It is noteworthy that simultaneous replacement of both chlorine atoms was never detected.

Table 1. Amination of 7,8-dichloro compound **1**



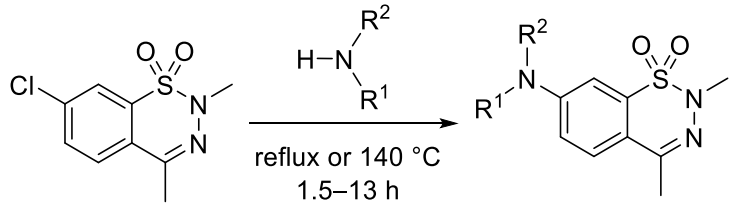
Entry	Amine (R^1R^2NH)	Products (isolated yields)	
1	morpholine	**2a** (49%)	**3a** (20%)
2	*N*-methylpiperazine	**2b** (46%)	**3b** (33%)
3	pyrrolidine	**2c** (71%)	**3c** (8%)

4	piperidine	**2d** (46%)	**3d** (40%)
5	2-aminoethanol	**2e** (24%)	**3e** (54%)
6	benzylamine	**2f** (n.i.)	**3f** (83%)
7	hexylamine	**2g** (5%)	**3g** (80%)
8	cyclohexylamine	**2h** (5%)	**3h** (88%)
9	diisopropylamine	n.r.	
10	aniline	n.r.	

n.i. = not isolated; n.r. = no reaction was observed

Amination of 7-chloro-2,4-dimethyl-BTD (**4**, Table 2) and 8-chloro-2,4-dimethyl-BTD (**6**, Table 3) afforded 7-amino (**5**) and 8-amino (**7**) congeners, respectively, in good yields. The absence of the second chlorine atom (compared to compound **1**) was accompanied in most cases with longer reaction times.

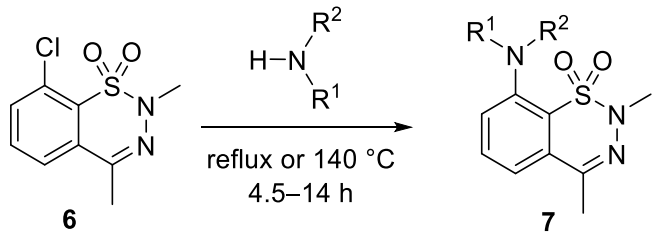
Table 2. Amination of 7-chloro compound **4**



4 **5**

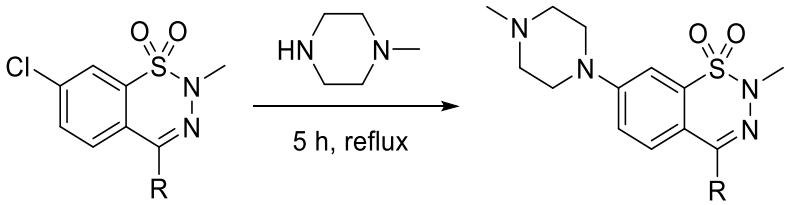
Amine (R^1R^2NH)	**Yield**
morpholine	**5a** (88%)
N-methylpiperazine	**5b** (69%)
pyrrolidine	**5c** (76%)
2-aminoethanol	**5d** (80%)
diisopropylamine	n.r.

Table 3. Amination of 8-chloro compound **6**



Amine (R^1R^2NH)	Yield
morpholine	**7a** (84%)
N-methylpiperazine	**7b** (90%)
pyrrolidine	**7c** (71%)
2-aminoethanol	**7d** (71%)

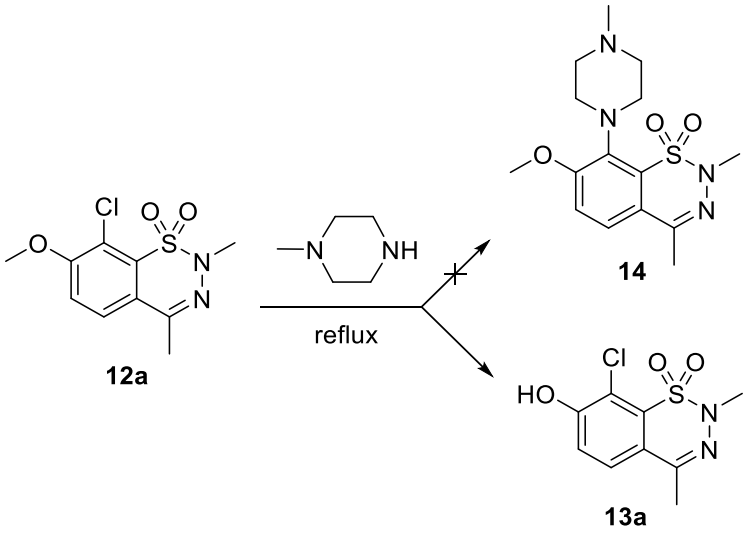
Interestingly, we found that the successful introduction of amines *via* nucleophilic substitution was limited to derivatives containing a *C*(4)-*N*(3) double bond and a methyl substituent at position *N*(2). 2-Unsubstituted and 3,4-dihydro counterparts suffered decomposition when refluxing in *N*-methylpiperazine. Otherwise, the reactions could be extended to 4-unsubstituted and 4-phenyl derivatives too. As representative examples, 7-chloro derivatives **8** and **9** were reacted with *N*-methylpiperazine in a similar manner (Scheme 1).



Scheme 1. Amination of 4-unsubstituted and 4-phenyl derivatives

Next, we turned our attention to derivatives containing a methoxy group besides the chloro substituent. To our surprise, in the reaction of 8-chloro-2,4-dimethyl-7-methoxy-BTD (**12a**) with *N*-methylpiperazine under the standard reaction conditions (neat, reflux), an *O*-

demethylation occurred leading to product **13a**, instead of substitution of the chlorine atom (**14**, Scheme 2).



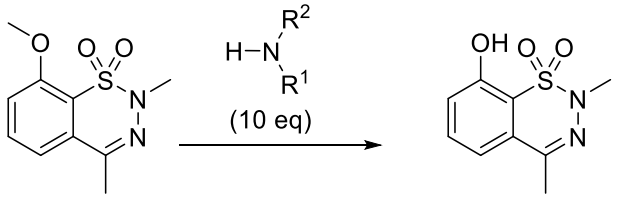
Scheme 2. Exploration of the reaction of 8-chloro-7-methoxy derivative **12a** with *N*-methylpiperazine

According to the literature, a large variety of methods have been elaborated for demethylation of aryl methyl ethers in order to provide reagents which allow selective transformation of polyfunctional molecules. Cleavage of aryl methyl ethers with Brønsted acids (hydrogen chloride, hydrogen iodide, hydrogen bromide) or pyridine hydrochloride requires drastic reaction conditions, temperatures up to 250 °C and long reaction times. The same reaction can be carried out with Lewis acids (preferably aluminium or boron halides) under substantially milder conditions.[15–19] Some basic reagents also have the ability to cleave aryl methyl ethers, e. g. sodium alkoxides,[20] sodium thiolates,[21,22] sodium bis(trimethylsilyl)amide and lithium diisopropylamide.[23] Furthermore, there are some examples in the literature of aryl methyl ether cleavage triggered by an amine. Nishioka et al. disclosed the *ortho*-selective demethylation of methoxy substituted benzoic acids and primary and secondary benzamides in the presence of piperazine (3 eq) in *N*,*N*-dimethylacetamide at 150 °C.[24] Later, the reaction was carried out in 1-methylpyrrolidin-2-one at 140 °C to prepare variously substituted *ortho*-hydroxybenzamides.[25] A regioselective aryl methyl ether cleavage was observed in the presence of

phenylethylamine at 200 °C.[26] *O*-Demethylation of 3,5-diaryl-4-methoxy-1-methylpyridine-2-one occurred in Et_3N/MeCN (2:1) at 80 °C.[27]

In our hands, running the demethylation of 8-methoxy derivative **12b** with various amines revealed that it was the fastest with *N*-methylpiperazine, maybe due to its higher boiling point compared to morpholine and pyrrolidine. The reactions were followed by LC-MS (Table 4).

Table 4. Investigation of demethylation of **12b** with amines

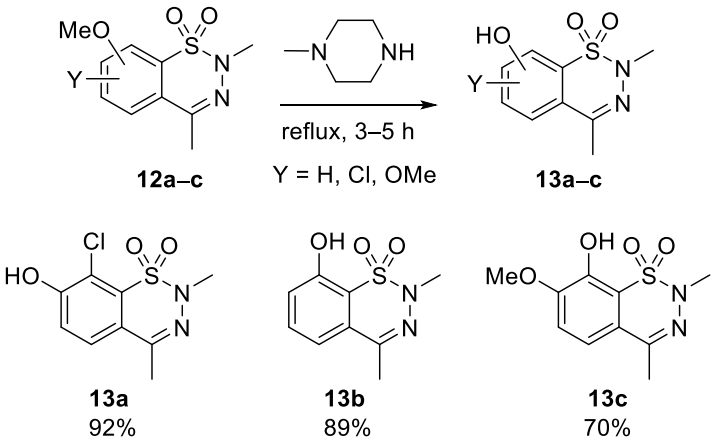


12b **13b**

Amine (R^1R^2NH)	**Temp. (°C)**	**Full conversion after**
N-methylpiperazine	138	3 h
morpholine	128	12 h[a]
pyrrolidine	87	15 h[a]

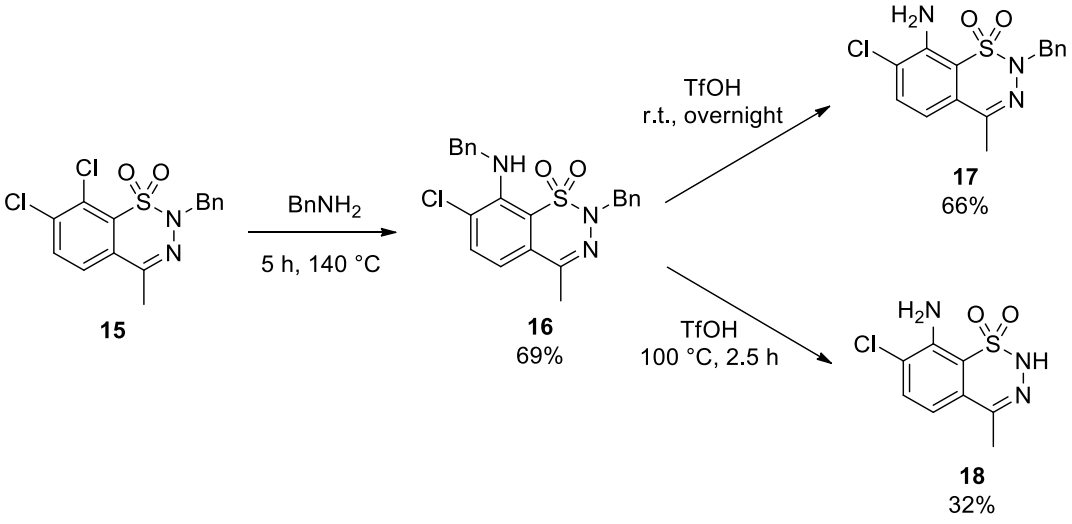
[a] Additional 10 eq amine was added after 9 h.

Then the optimized conditions were applied for the synthesis of phenols **13a**–**c** in good to excellent yields using *N*-methylpiperazine (Scheme 3). It is worth mentioning that this method is useful for 7- (**13a**) and 8-demethylation, too (**13b**). In addition, when starting from 7,8-dimethyl derivative **12c**, the dealkylation was selective, 8-hydroxy compound **13c** was the major product with 70% isolated yield, whereas demethylation at position 7 or at both positions were minor side-reactions. Cleavage of the *N*(2)-methyl group was not observed.



Scheme 3. Demethylation of methoxy derivatives **12a–c**

Although we were mainly interested in 2-alkyl derivatives, we also aimed at the synthesis of 2-unsubstituted BTDs bearing an amino group at the aromatic ring. Benzyl group seemed to be a protecting group promising to withstand the harsh conditions of the chlorine-amine exchange reaction. Reaction of **15**[6] with benzylamine gave selectively 8-benzylamino-7-chloro compound **16** bearing two benzyl groups (Scheme 4). The amino function at position 8 could be selectively deprotected at room temperature with trifluoromethanesulfonic acid (triflic acid, TfOH) resulting in compound **17**, whereas double debenzylation occurred in one pot at 100 °C to give **18** in 32% yield. Compounds **17** and **18** are useful intermediates for the introduction of various pharmacophores.



Scheme 4. Synthesis of *N*(2)-unsubstituted-8-amino-BTD **18**

Structure elucidation of the new compounds described above is based on the molecular formulas obtained by HRMS and on detailed NMR studies. Full ^{1}H and ^{13}C signal assignment was performed by means of comprehensive one- and two-dimensional NMR methods using widely accepted strategies.[28,29] ^{1}H assignments were accomplished using the general knowledge of chemical shift dispersion with the aid of the ^{1}H-^{1}H coupling pattern. NMR structure elucidation and signal assignment of regioisomers **2** and **3** is exemplified here on derivatives **2a** and **3a** (Fig. 3 and Supporting Information pages S2–5).

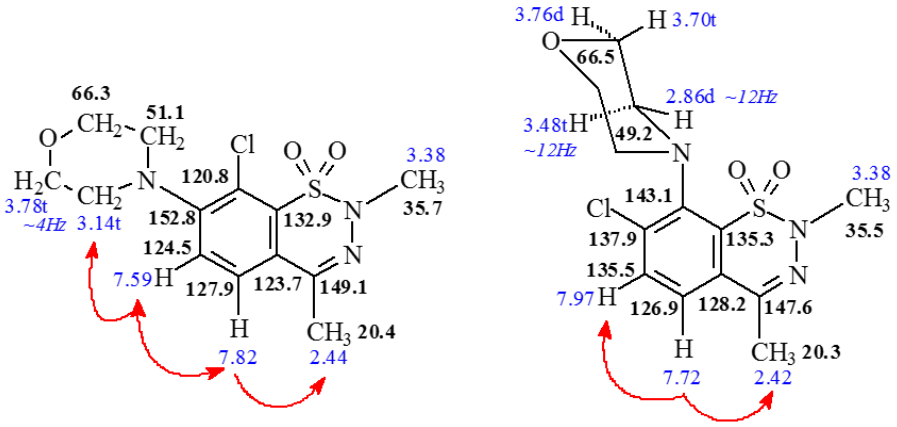


Figure 3. Structures of regioisomers **2a** and **3a**. (Blue numbers refer to ^{1}H, while black ones to ^{13}C chemical shifts. Cursive blue values denote characteristic *J*(H,H) couplings in Hz. The red arrows indicate steric proximities detected by selective one-dimensional selNOE experiments.)

In case of **2a** (Supporting Information, pages S2–3), one-dimensional selective NOE (selNOE) measurement showed a proximity between 5-H (δ 7.82d) and 4-CH_3 (δ 2.44s), whereas selNOE on 6-H (δ 7.59d) gave a response on the $N(CH_2)_2$ signal (δ 3.14t) of the morpholine ring, proving that the latter is connected to the C-7 atom. The triplet multiplicity of $N(CH_2)_2$ and $O(CH_2)_2$ signals shows a fast inversion of the chair conformer, switching axial and equatorial positions, and a nitrogen inversion occurs pushing the BTD ring to the preferred equatorial position. The HSQC spectrum resulted in the unambiguous assignment of C-H units, whereas the assignment of quaternary carbon atoms were

supported by HMBC measurements. Otherwise, 5-H/C-7 and 6-H/C-8 cross-peaks in the HMBC spectrum (Supporting Information, page S3) justify the structure, as well. The occasionally appearing doublets give the values of ^{1}J(CH).

For **3a** (Supporting Information, pages S4–5), selNOE proved that the position of 5-H and 6-H signals (7.72 and 7.97 ppm, respectively) was changed in comparison to compound **2a**. When the morpholino group is attached to C-8, the triplet multiplicity of NCH_2 and OCH_2 signals altered significantly. Due to the steric hindrance (the ring is stuck between the 7-Cl and SO_2 groups), a fast ring inversion cannot take place anymore. The geminal methylene hydrogen atoms are now diastereotopic, thus separated H_{ax} (t, $^{3}J(H_{ax},H_{ax})$ ~ 12 Hz) and H_{eq} (d, ^{2}J(H,H) ~ 12 Hz) signals can be observed. The $^{3}J(H_{eq},H_{eq})$ and $^{3}J(H_{ax},H_{eq})$ couplings of ca. 3 Hz result in line broadening. It should be mentioned that these phenomena were observed for each regioisomeric pair (**2** and **3**), and by using the above approach, an unambiguous structure determination could be carried out in each case.

Conclusion

The substitution of *N*(2)-alkyl-BTDs bearing chlorine atom(s) at the aromatic ring was described with various amines under neat conditions. Monochloro derivatives (either 7-Cl or 8-Cl) underwent a clean reaction, whereas the observed regioselectivity was discussed in the case of 7,8-dichloro compounds. Structure determination of the regioisomers was carried out using selNOE and detailed 2D NMR techniques. A protecting group strategy employing an *N*(2)-benzyl group was also elaborated to synthesize *N*(2)-unsubstituted derivatives, using triflic acid for the removal of benzyl moiety. 7- or 8-Hydroxy-BTDs were prepared *via* the demethylation of the corresponding methoxy-BTDs simply by refluxing in *N*-methylpiperazine. The new compounds synthesized are either themselves interesting for pharmacological studies or can be used for further functionalization.

Supporting information

Synthetic procedures leading to new compounds **2a**–**e**,**g**,**h**, **3a**–**h**, **5a**–**d**, **7a**–**d**, **10**, **11**, **12c**, **13a**–**c**, **16**–**18**, and detailed NMR structure elucidation (including ^{1}H and ^{13}C NMR, DEPTQ, HSQC, HMBC and selNOE spectra) can be found in the Supporting Information.

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