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## Fluorinated triazole-containing sphingosine analogues. Syntheses and *in vitro* evaluation as SPHK inhibitors†

Margarita Escudero-Casao,<sup>a</sup> Adrià Cardona,<sup>a</sup> Raúl Beltrán-Debón,<sup>b</sup> Yolanda Díaz,<sup>a</sup> M. Isabel Matheu<sup>a</sup> and Sergio Castellón<sup>a</sup>

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Sphingosine analogues with a rigid triazole moiety in the aliphatic chain and systematic modifications in the polar head and different degrees of fluorination at the terminus of the alkyl chain were synthesized from a common alkynyl aziridine key synthon. This key synthon was obtained by enantioselective organo-catalyzed aziridination and it was subsequently ring opened in a regioselective manner in acidic medium. Up to 16 sphingosine analogues were prepared in a straightforward manner. The *in vitro* activity of the obtained products as SPHK1 and SPHK2 inhibitors was evaluated, displaying comparable activity to that of DMS.

## Introduction

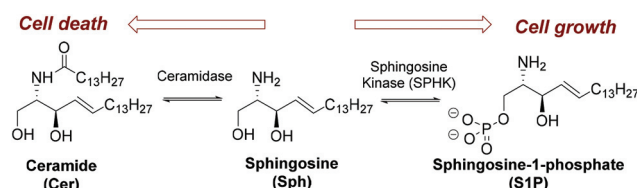
Sphingosine kinase (SPHK) is a key regulator of the sphingolipid rheostat (Scheme 1),<sup>1</sup> a dynamic balance between ceramide (Cer) and sphingosine 1-phosphate (S1P) that guides the cell toward either an apoptotic or a survival process (Scheme 1).<sup>2,3</sup> SPHK catalyses the ATP-dependent phosphorylation of sphingosine (Sph) to generate S1P and exists in two isoforms, SPHK1 and SPHK2.<sup>4</sup> The interest in SPHK inhibitors<sup>5</sup> as potential drugs stems from the fact that SPHK1 is usually up-regulated in several forms of cancer and that its genetic ablation leads to the sensitization of cancer cells to chemotherapeutic agents and its implication in several diseases.<sup>6,7</sup> Similarly, different pieces of evidence support the role of SPHK2 in cancer.<sup>8</sup>

There has been extensive focus on the development of effective sphingosine kinase inhibitors (SKIs) in recent years and the progress in this area has been recently reviewed.<sup>6,9</sup> Among the described SKIs derived from sphingolipids (Fig. 1), the following SKIs stand out: safingol<sup>10</sup> (saturated sphingosine analog with the unnatural *threo* stereochemistry), *N,N*-dimethylsphingosine (DMS),<sup>11</sup> short-chain sphinganine (C12) and 3-fluorosphingosine analogues,<sup>12</sup> *N*-derivatized analogues such as phenethyl isothiocyanate derivatives,<sup>13</sup> guanidine

analog LCL351,<sup>14</sup> *N*-methylated SK-I,<sup>15</sup> the aromatic analogue SG-12,<sup>16</sup> enigmol (where the 1-OH of Sph has been shifted to position 5),<sup>17</sup> phytosphingosine,<sup>18</sup> and FTY720,<sup>19</sup> and its vinyl phosphonate derivatives.<sup>20</sup>

Quite recently, the structures of SPHK1 in complexes with ADP, and some inhibitors<sup>21</sup> have been disclosed. The hydrophilic head group of the sphingosine is situated at the cleft between two N- and C-domains, leading to hydrogen-bond interactions with Asp and Ser residues. The hydrophobic alkyl chain is accommodated in a J-shaped tunnel, lined by the side chains of mostly nonpolar residues.

Despite the wide array of compounds developed so far and the recent breakthroughs<sup>22</sup> in the structural and functional characterization of SPHK, synthesis may provide new architectures that help in gaining insight into the regulation of the complex mechanism that governs S1P metabolism. In this context, the aim of this work is the syntheses of new lipidic compounds as potential SKIs. The structures proposed for this purpose retain the polar part of the parent compound, sphingosine, maintaining the key aminodiol moiety. The head-group will be attached to a triazole core, mimicking the *trans* double bond present in sphingosine<sup>23</sup> and allowing additional



Scheme 1 Ceramide/sphingosine-1-phosphate rheostat.

<sup>a</sup>Departament de Química Analítica i Química Orgànica, Universitat Rovira i Virgili, C/Marcel·lí Domingo nº 1, 43007 Tarragona, Spain. E-mail: maribel.matheu@urv.cat

<sup>b</sup>Departament de Bioquímica i Biotecnologia, Universitat Rovira i Virgili, C/Marcel·lí Domingo nº 1, 43007 Tarragona, Spain

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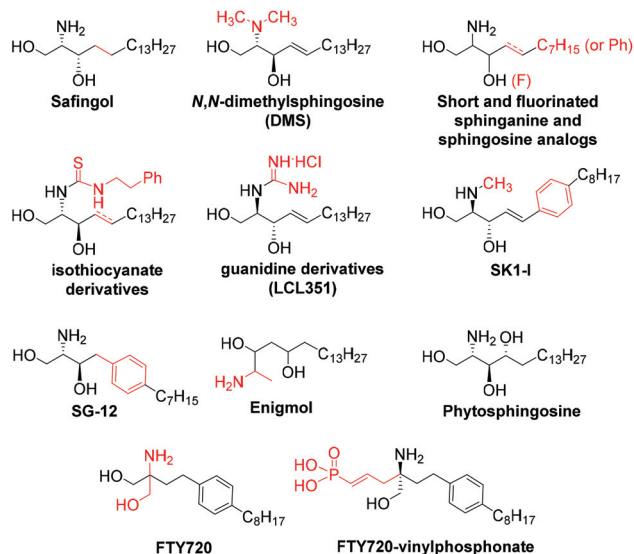


Fig. 1 SPHK inhibitors derived from sphingolipids.

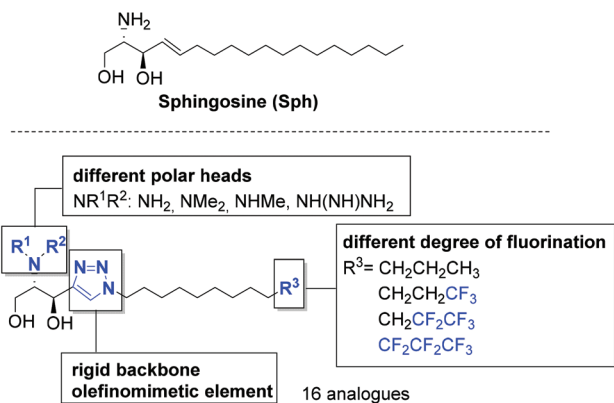
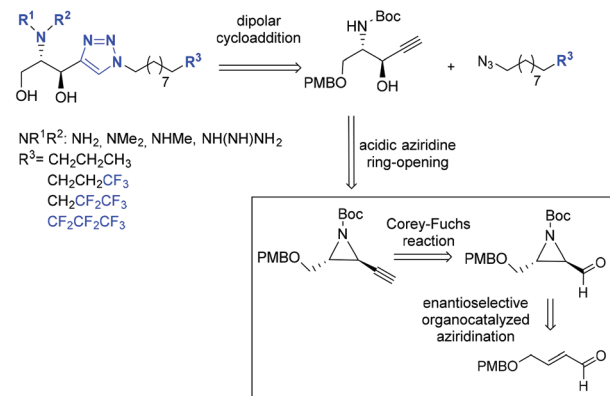


Fig. 2 Structural modifications of sphingosine proposed in this work.

interactions (Fig. 2). The triazole unit, in turn, will be appended to a modified lipophilic end to enhance hydrophobic interactions with the pocket of SPHK1. Additional SPHK1 affinity might be anticipated to be increased through derivatization of the amino group.

Considering our experience in the field of the synthesis of sphingoid bases,<sup>24</sup> and aiming to explore new methodologies for obtaining sphingosine derivatives, we envisioned the synthesis of the proposed analogues by a click reaction from a common intermediate, obtained from an alkynyl aziridine (Scheme 2).

Alkynyl aziridines are useful intermediates in many synthetic processes and they have been synthesized through a variety of protocols.<sup>25</sup> For some of them the asymmetric version has been reported. Thus, enantioenriched alkynylaziridines have been prepared from chiral alkynylamino alcohols by an intramolecular substitution reaction,<sup>26</sup> by addition of guanidium ylides to aldehydes,<sup>27</sup> by catalyzed nitrene addition



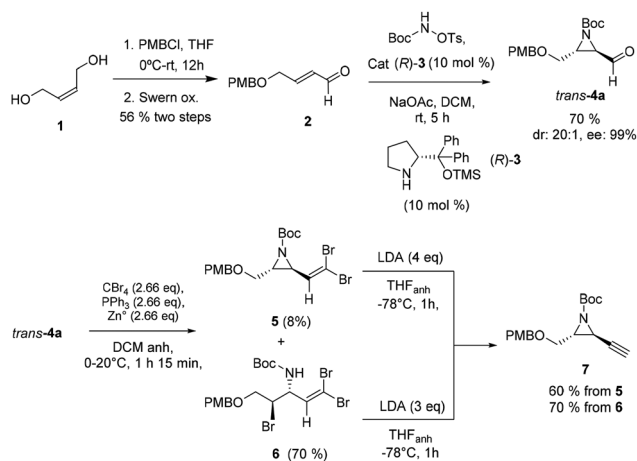
Scheme 2 Retrosynthetic proposal: organocatalyzed aziridination and the Corey–Fuchs reaction as the key steps.

to alkynyl olefins,<sup>28</sup> and by catalyzed addition of carbenes to imines.<sup>29</sup> Yudin reported that alkynyl aziridines could be obtained from alkynyl aldehydes by one-carbon homologation.<sup>30</sup>

Here we report that enantioenriched alkynylaziridines can be accessed *via* a proline organocatalyzed aziridination reaction of  $\alpha,\beta$ -unsaturated aldehydes followed by a homologation reaction (Scheme 2). Regioselective ring opening of this common intermediate followed by triazole click chemistry with the corresponding fatty alkyl azides furnishes a library of sphingosine analogues bearing a triazole unit containing oligofluorinated alkyl chains. This library may be extended by selected derivatizations at the amino moiety.

## Results and discussion

Starting  $\alpha,\beta$ -unsaturated aldehyde substrate **2**<sup>31</sup> for the organocatalyzed aziridination reaction was first synthesized according to the literature *via* monoprotection of diol **1** as the *p*-methoxybenzyl ether<sup>32</sup> and subsequent Swern oxidation in a 56% global yield (Scheme 3). The enantioselective organocatalytic



Scheme 3 Synthesis of ethynyl aziridine **7** from diol **1**.

aziridination<sup>33</sup> of the  $\alpha,\beta$ -unsaturated aldehyde **2** with *O*-tosyl-*N*-*tert*-butoxycarbonyl-hydroxylamine catalyzed by TMS-protected diphenylprolinol (*R*)-**3**<sup>34</sup> provided the desired  $\beta$ -formyl aziridine **4a** in a 70% yield with 20:1 dr and 99 ee%. The enantiomeric excess was established *via* the formation of the corresponding vinyl derivative *via* the Wittig reaction (see the ESI†).

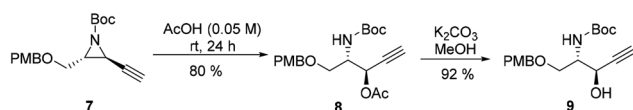
With aldehyde **4a** in hand, we set up one-carbon homologation to render the alkyne moiety. When aldehyde **4a** was treated under Corey–Fuchs conditions<sup>35</sup> with  $\text{CBr}_4$ , triphenylphosphine and zinc dust in dichloromethane the corresponding dibromoalkene **5** was obtained only in an 8% yield (Scheme 3), the tribrominated alkene **6** being the main product (70% yield). Product **6** might result from the bromide ring opening of aziridine **4a**.<sup>36</sup>

Gratifyingly, both products, **5** and **6**, when subjected to LDA treatment led to the corresponding ethynylaziridine **7** *via* metal-halogen exchange and ulterior  $\alpha$ -elimination,<sup>37</sup> and from **6** through an additional ring closing process in the basic media.

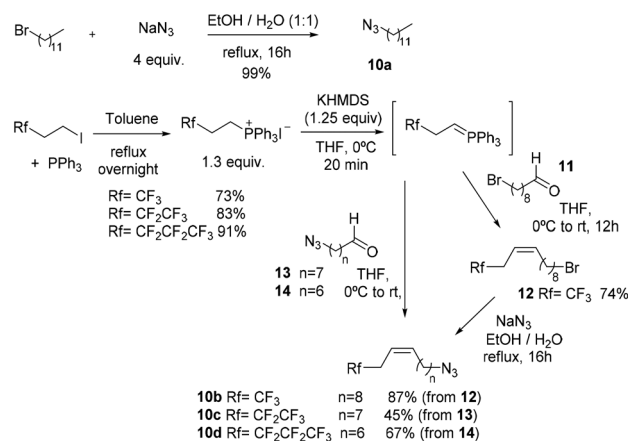
Ring opening of aziridine **7** with acetic acid at room temperature followed by basic hydrolysis of the acetate group in **8** furnished the *N*-protected amino alcohol **9** in excellent yield (Scheme 4). The observed regioselectivity can be rationalized considering the selective nucleophilic attack at the propargylic position (see ref. 25 for a general review dealing with the synthesis and opening of alkynyl (and vinyl) aziridines). This effect has also been described in the ring-opening reactions of vinyloxirane and activated vinylaziridine derivatives.<sup>38</sup>

In order to perform click triazole syntheses, azides **10a–d** were synthesized. 1-Azidododecane **10a** was obtained quantitatively from 1-bromododecane by treatment with sodium azide in a 1:1 mixture of refluxing EtOH:H<sub>2</sub>O. Azide **10b** was synthesized from 9-bromononanal **11** *via* the Wittig reaction with the corresponding trifluorinated phosphorus ylide and ulterior bromide displacement with sodium azide (Scheme 5). For practical reasons,<sup>39</sup> azides **10c** and **10d** were synthesized by the Wittig reaction with the corresponding azido aldehydes **13** and **14**. All aldehydes were obtained from the respective alcohols by Swern oxidation.

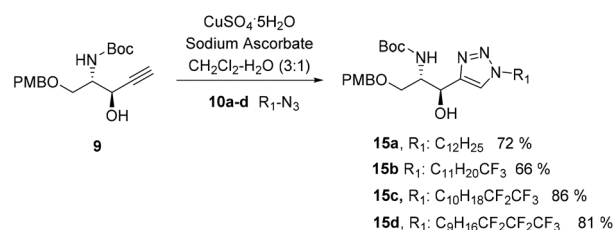
A copper catalysed cycloaddition reaction of azides **10a–d** with the alkyne **9** previously prepared afforded triazoles **15a–d** in yields ranging from 66% to 86% (Scheme 6). With these protected triazole-based sphingosine analogues in hand, the corresponding modifications in the amine functionality were carried out. Thus, the preparation of the non-fluorinated *N*-monomethyl amine **18a** was accomplished by reduction of the carbamate group and ulterior *p*-methoxybenzyl ether deprotection. Inverting the sequence of events, as was done for the fluorinated analogues (see below), leads in this case to



Scheme 4 Synthesis of intermediate **9** by aziridine ring opening.



Scheme 5 Synthesis of azides **10a–d**.



Scheme 6 Azide-alkyne cycloaddition.

worse yields. For obtaining fluorinated *N*-methyl derivatives **18b–d** an additional double bond reduction step was required. This transformation was performed using **15b–d** with Pd/C, H<sub>2</sub>, with concomitant PMB hydrogenolysis, and the Boc group was subsequently reduced (Scheme 7). Boc deprotection of compounds **17b–d** led to free amino analogues **19b–d**. Non-fluorinated aminodiols **19a**, in turn, can be directly obtained from the non-olefinated compound **15a** by simultaneous Boc and PMB deprotection with TFA.

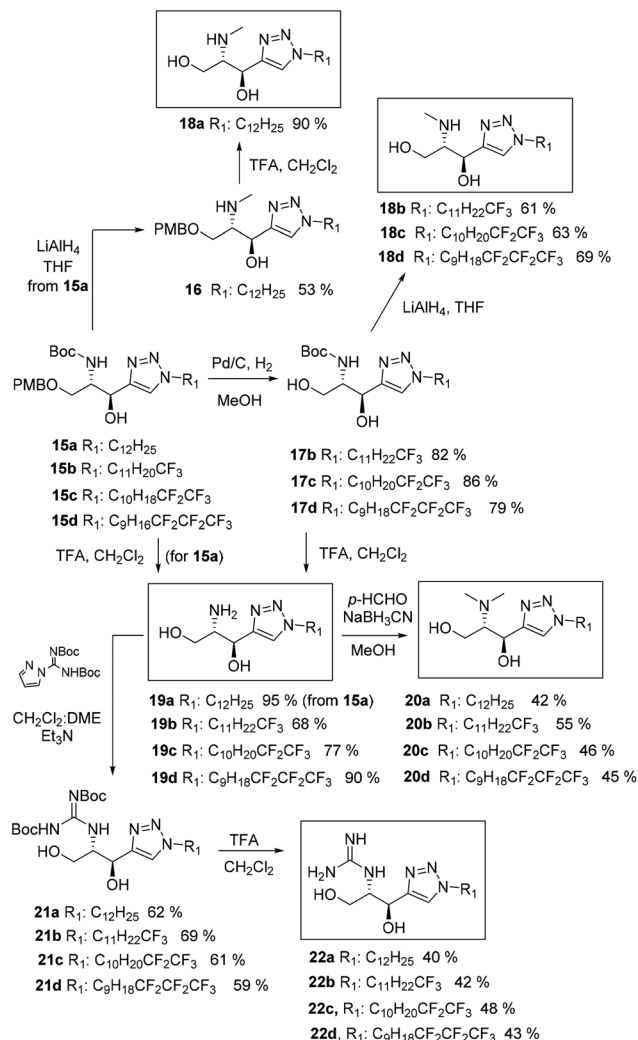
*N,N*-Dimethyl derivatives **20a–d** were synthesized from **19a–d** by reductive amination with *p*-formaldehyde (Scheme 7). The synthesis of *N*-guanidine sphingosines was accomplished by reaction of amines **19a–d** with *N,N'*-di-Boc-1*H*-pyrazole-1-carboxiamidine to afford *N*-Boc derivatives **21a–d**, followed by deprotection with a 1:1 mixture of TFA/CH<sub>2</sub>Cl<sub>2</sub>.

Although purification of guanidine derivatives was performed under basic conditions, and despite that an ulterior treatment with aqueous NaOH had been carried out, compounds **22b–d** were obtained as the trifluoroacetate salts.

The half maximal inhibitory concentration (IC<sub>50</sub>) of each compound was determined using an *in vitro* time-resolved fluorescence energy transfer (TR-FRET) analysis (Table 1 and Fig. 1 and 2 of the ESI†). This experiment was performed independently for each kinase and dimethyl sphingosine was used as a reference.

None of the compounds showed a higher inhibitory activity than the reference DMS, but two of them showed an IC<sub>50</sub> value





**Scheme 7** Last steps and *N*-derivatization for the syntheses of target triazole analogues.

close to DMS. Thus, the non-fluorinated guanidine derivative **22a** showed an IC<sub>50</sub> = 7.9 μM for SPHK2 and the pentafluoro *N*-monomethyl compound **18c** showed an IC<sub>50</sub> = 30.0 μM for SPHK1. However, these activities were not selective and these compounds showed also inhibitory activity against the other kinase.

More interestingly, some compounds actually showed modest but selective inhibitory activity for SPHK2 (free amino trifluoromethyl and heptafluoro compounds **19b** and **19d** as well as *N,N*-dimethylamino fluorinated derivatives **20b**, **20c** and **20d**). As a general trend, the family of compounds constituted of heptafluoroderivatives (**18d**, **19d**, **20d** and **22d**) showed a good and selective inhibitory activity against SPHK2, the *N,N*-dimethyl derivative **22d** being the best compound in this series in terms of activity/selectivity.

The presence of polyfluorinated alkyl fragments in a compound is known to affect the lipophilicity and conformational rigidity of the parent molecule along with other effects.<sup>40</sup> In our case, the terminal heptafluoropropyl unit can confer a

**Table 1** IC<sub>50</sub> values of compounds **18a–d**, **19a–d**, **20a–d**, and **22a–d** and the reference, DMS, for each sphingosine kinase

Inhibitor	SPHK1	SPHK2	Inhibitor	SPHK1	SPHK2
<b>18a</b> R <sub>1</sub> : C <sub>12</sub> H <sub>25</sub>	61.5	22.9	<b>20a</b> R <sub>1</sub> : C <sub>12</sub> H <sub>25</sub>	110.2	22.2
<b>18b</b> R <sub>1</sub> : C <sub>11</sub> H <sub>22</sub> CF <sub>3</sub>	48.9	41.9	<b>20b</b> R <sub>1</sub> : C <sub>11</sub> H <sub>22</sub> CF <sub>3</sub>	—	56.8
<b>18c</b> R <sub>1</sub> : C <sub>10</sub> H <sub>20</sub> CF <sub>2</sub> CF <sub>3</sub>	30.0	39.5	<b>20c</b> R <sub>1</sub> : C <sub>10</sub> H <sub>20</sub> CF <sub>2</sub> CF <sub>3</sub>	—	70.8
<b>18d</b> R <sub>1</sub> : C <sub>9</sub> H <sub>18</sub> CF <sub>2</sub> CF <sub>2</sub> CF <sub>3</sub>	51.6	10.7	<b>20d</b> R <sub>1</sub> : C <sub>9</sub> H <sub>18</sub> CF <sub>2</sub> CF <sub>2</sub> CF <sub>3</sub>	—	15.6
<b>19a</b> R <sub>1</sub> : C <sub>12</sub> H <sub>25</sub>	97.1	25.6	<b>22a</b> R <sub>1</sub> : C <sub>12</sub> H <sub>25</sub>	41.9	7.9
<b>19b</b> R <sub>1</sub> : C <sub>11</sub> H <sub>22</sub> CF <sub>3</sub>	—	40.5	<b>22b</b> R <sub>1</sub> : C <sub>11</sub> H <sub>22</sub> CF <sub>3</sub>	—	—
<b>19c</b> R <sub>1</sub> : C <sub>10</sub> H <sub>20</sub> CF <sub>2</sub> CF <sub>3</sub>	—	—	<b>22c</b> R <sub>1</sub> : C <sub>10</sub> H <sub>20</sub> CF <sub>2</sub> CF <sub>3</sub>	51.1	19.1
<b>19d</b> R <sub>1</sub> : C <sub>9</sub> H <sub>18</sub> CF <sub>2</sub> CF <sub>2</sub> CF <sub>3</sub>	—	28.5	<b>22d</b> R <sub>1</sub> : C <sub>9</sub> H <sub>18</sub> CF <sub>2</sub> CF <sub>2</sub> CF <sub>3</sub>	60.0	18.1
DMS	27.3	3.8			

Values are expressed as concentrations (μM), and no value (—) means low or no inhibitory activity detected.

lower conformational mobility to this family of sphingolipid analogues, which might make a proper fitting of the alkyl chain into the J-shaped tunnel of SPHK1 difficult. This fact could explain the observed selective inhibitory activity against SPHK2 if the cavity of this kinase was straighter than that of SPHK 1. However, the crystal structure of SPHK2 has not been elucidated yet, so this hypothesis cannot be confirmed. Nonetheless, these results postulate heptafluoro-derivatization as a starting point for future SPHK2 selective inhibitors.

## Conclusions

In summary, we have reported an efficient method for obtaining enantioenriched alkynylaziridines by a proline organocatalyzed aziridination reaction of α,β-unsaturated aldehydes followed by a homologation reaction. This approach has allowed easy access to a library of 16 sphingosine analogues bearing a common triazole motif, including systematic modifications at the amino moiety and a different degree of fluorination at the end of the alkyl chain. The products obtained showed comparable *in vitro* activity to that of DMS as SPHK1 and SPHK2 inhibitors, although the family constituted of a heptafluoro tail exhibits selective inhibitory activity towards SPHK2, postulating this derivatization as a starting point for future SPHK2 selective inhibitors.



## Conflicts of interest

There are no conflicts to declare.

## Acknowledgements

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