Tetrahedron Letters 54 (2013) 1938–1942

Contents lists available at SciVerse ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

# 2,5-Bis-(sulfonyl)pyrazines as unprecedented building blocks and their $S_NAr$ reactions

Jie Jack Li [a], Wei Meng [b], Shung Wu [b], Yong-Jin Wu [c], Jason Guernon [c], Martin P. Allen [a], Michael M. Miller [a,*], Peter T. Cheng [b], Bang-chi Chen [a]

[a] Medicinal Chemistry, Bristol-Myers Squibb Company, Route 206 & Province Line Road, Princeton, NJ 08543, United States
[b] Medicinal Chemistry, Bristol-Myers Squibb Company, 311 Pennington-Rocky Hill Road, Pennington, NJ 08534, United States
[c] Medicinal Chemistry, Bristol-Myers Squibb Company, 5 Research Parkway, Wallingford, CT 06492, United States

ARTICLE INFO

*Article history:*
Received 27 December 2012
Revised 22 January 2013
Accepted 24 January 2013
Available online 4 February 2013

*Keywords:*
Pyrazine
$S_NAr$ reactions
Bis-(sulfonyl)pyrazines

ABSTRACT

Previously unknown 2,5-bis-sulfonylpyrazines are prepared and their $S_NAr$ reactions are investigated. When 2 equiv of thiols are employed, the corresponding bis-thiopyrazines are obtained exclusively. However, phenols or alkoxides gave rise to only the corresponding mono-substituted aryloxy- or alkoxy-sulfonylpyrazines in excellent yields. A carbon nucleophile prepared by treating malonate with NaH also produced the corresponding mono-sulfonylpyrazines. Aliphatic amines and anilines only provided the mono-anilino-sulfonylpyrazines in poor to moderate yields.



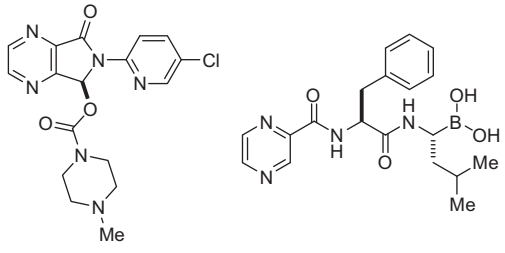
Pyrazines are not common in nature. However, the importance of pyrazine as the bioisostere for either benzene or pyridine rings has been manifested by eszopiclone (Fig. 1, **1**, Lunesta)[1] as a synaptic γ-aminobutyric acid (GABA) receptor modulator for the treatment of insomnia. Another pyrazine-containing drug is bortezomib (**2**, Velcade), an intravenously administered first-in-class proteasome inhibitor for the treatment of patients with multiple myeloma (MM) who had received at least two prior therapies.[2]

Sulfonylpyrazines, on the other hand, have emerged as important moieties in pharmaceutical agents. Conspicuously, (methylsulfonyl)pyrazine **3** is a cell proliferation inhibitor[3] and sulfonylpyrazine **4** is a prostacyclin ($PGI_2$) receptor agonist, potentially used for the treatment of various vascular diseases (Fig. 2).[4] In addition, (methylsulfonyl)pyrazine **5** is an adenosine antagonist,[5] and sulfonylpyrazine **6** was investigated as an insecticide, acaricide, or nematicide.[6]

During our drug discovery programs, we have developed a novel methodology for preparing 2,5-bis-sulfonylpyrazines from commercially available 2,5-bis-bromopyrazine (**7**). Surprisingly, neither 2,5-bis-alkylsulfonylpyrazines nor 2,5-bis-arylsulfonylpyrazines were previously known in the literature.

We prepared 2,5-bis-(sulfonyl)pyrazines **9** from readily commercially available 2,5-bis-bromopyrazine (**7**). As shown in Scheme 1, disulfide **8a** was obtained by refluxing **7** with 10 equiv of sodium methanethiolate in DMF overnight.[3] Oxidation of disulfides **8a** to bis-sulfones **9a** was initially accomplished by using 6 equiv of Oxone® in *i*-PrOH/$H_2O$ (5:1) at room temperature in nearly quantitative yields.[7] However, the reaction was heterogeneous and the workup was cumbersome because of large amounts of Oxone® used. An alternative oxidation employing hydrogen peroxide in acetic acid is homogeneous and operationally more convenient.[8]

With bis-sulfone **9a** in hand, we explored its ability to undergo $S_NAr$ reactions with a wide variety of nucleophiles. As shown in Scheme 2, when 4-fluorophenol was employed, the $S_NAr$ reaction halted after 1 equiv of the nucleophile was added to the pyrazine ring. After the phenyl–pyrazinyl ether **10** is formed, the pyrazine ring is deactivated because of the strong electron-donating nature



**1**, eszopiclone (Lunesta) **2**, bortezomib (Velcade)

**Figure 1.** Pyrazine-containing drugs on the market.

* Corresponding author. Tel.: +1 609 252 3238.
*E-mail address:* michael.miller@bms.com (M.M. Miller).

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http://dx.doi.org/10.1016/j.tetlet.2013.01.106

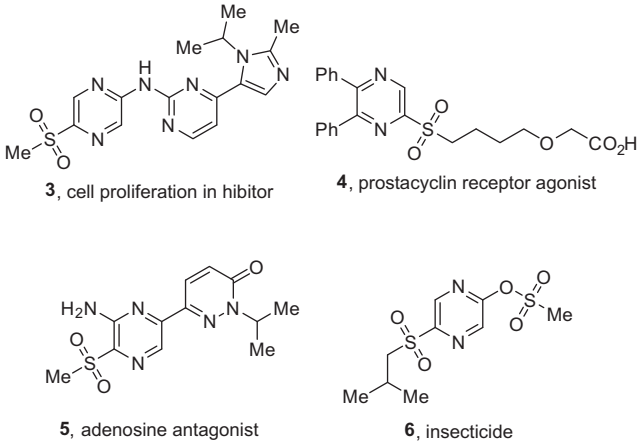
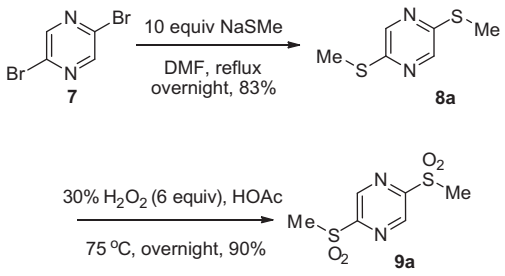
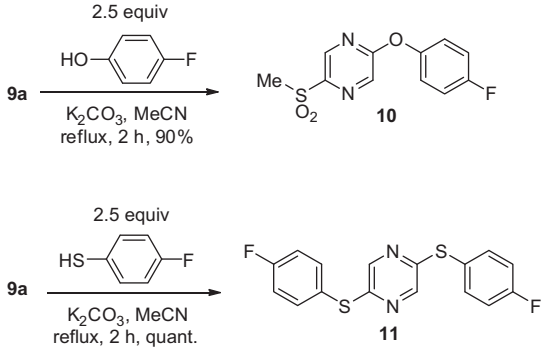


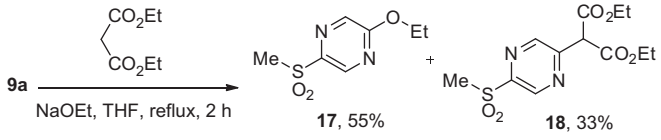

**Figure 2.** Sulfonylpyrazine-containing compounds in medicinal chemistry.




**Scheme 1.** Two-step preparation of 2,5-bis-(methysulfonyl)pyrazine **9a**.

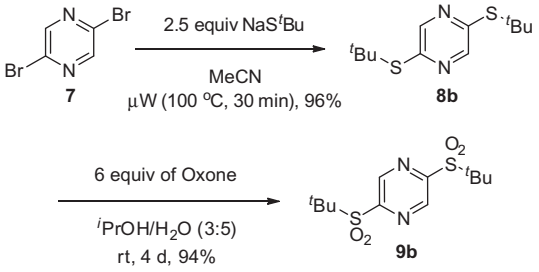



**Scheme 2.** $S_NAr$ reactions of **9a** with phenol and thiophenol.

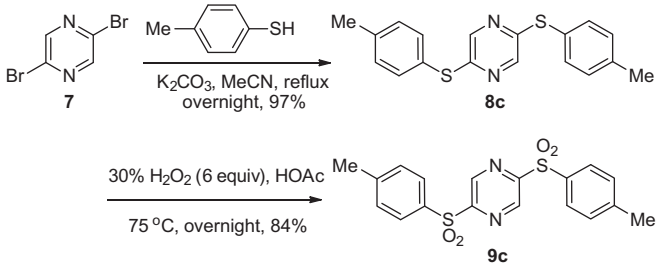



**Scheme 3.** $S_NAr$ reactions of **9a** with sodium ethoxide and malonate.

of the oxygen atom. Therefore, even though an excess amount of 4-fluorophenol (2.5 equiv) was used, the mono-$S_NAr$ product was the sole product produced, giving rise to **10** in 90% isolated yield.[9] In contrast, when 2.5 equiv of 4-fluorothiophenol was used as the nucleophile, bis-sulfide **11** was isolated exclusively. Interestingly, employing only 1 equiv of 4-fluorothiophenol, the mono-substitution product **12** was produced as the sole product (Table 1, entry




**Scheme 4.** Two-step preparation of 2,5-bis-*t*-butylsulfonylpyrazine **9b**.



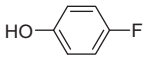
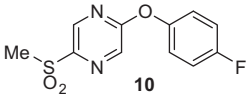
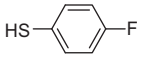
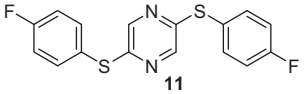
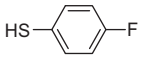
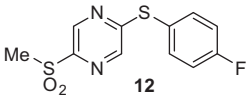
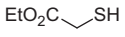
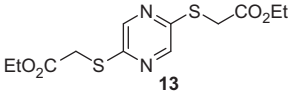
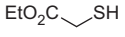
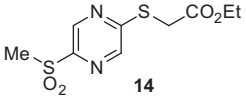
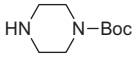
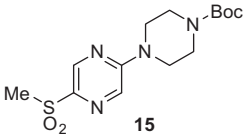
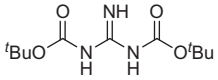
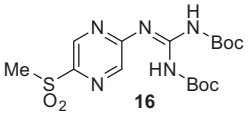
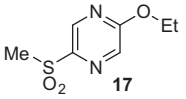
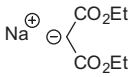
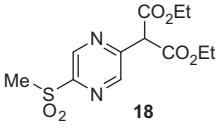

**Scheme 5.** Two-step preparation of 2,5-bis(tolylsulfonyl)pyrazine **9c**.

3). In the same vein, the $S_NAr$ reaction of **9a** with 2.5 equiv of ethyl 2-mercaptoacetate, perhaps not surprisingly, afforded the double $S_NAr$ reaction product, bis-sulfide **13**. Again, employing only 1 equiv of ethyl 2-mercaptoacetate, the mono-substitution product **14** was produced in 69% yield, along with concurrent formation of 29% of **13**.[10] Unfortunately, the yields for the $S_NAr$ reactions of the nitrogen nucleophiles were poor to moderate. When the aliphatic amine *tert*-butyl piperazine-1-carboxylate was used, only 37% of the mono-substituted pyrazine **15** was isolated. The bis-substitution product was not isolated presumably because of its extremely low solubility. When a bis-Boc-guanidine was employed as the nucelophile, the mono-substituted product **16** was isolated. Our methodology was also found to have additional limitations in aliphatic alcohols. No reaction was observed when aliphatic alcohols were used as nucleophiles. However, when sodium ethoxide was used, 2-ethoxy-5-(methylsulfonyl)pyrazine (**17**) was isolated in 84% yield. In addition, when the $S_NAr$ reaction of **9a** with a carbon nucleophile was initially carried out using diethyl malonate treated with 1 equiv of NaOEt, a mixture of 2-ethoxy-5-(methylsulfonyl)pyrazine (**17**) and diethyl 2-(5-(methylsulfonyl)pyrazin-2-yl)malonate (**18**) was afforded in 55% and 33% yields, respectively (Scheme 3). This is a reflection of the fact that NaOEt is more nucleophilic than sodium malonate. Although when sodium malonate was derived by the treatment of diethyl malonate with 1 equiv of NaH, 2-(5-(methylsulfonyl)-pyrazin-2-yl)malonate (**18**) was isolated as the sole product in 86% yield. This was the case even when 2 equiv of the nucleophile was employed.[11]

Meanwhile, 2,5-bis-*t*-butylsulfonylpyrazine (**9b**) was prepared in a similar fashion to that described for **9a** (Scheme 4). Double $S_NAr$ displacement of 2,5-bis-bromopyrazine (**7**) with 2.5 equiv of sodium *t*-butanethiolate upon microwave irradiation (MeCN, 30 min, 100 °C) provided disulfide **8b**. Oxidation of disulfide **8b** to bis-sulfone **9b** was accomplished by using 6 equiv of Oxone® in *i*-PrOH/$H_2O$ at room temperature over 4 days. The prolonged reaction time may be a reflection of the steric hindrance that the *t*-butyl group exerted.

The $S_NAr$ reactions of bis-sulfones **9b** with a wide variety of nucleophiles have been explored. Compared to **9a**, a similar trend of reactivity for **9b** was observed. As shown in Table 2, sulfur

**Table 1**
$S_NAr$ reactions of 2,5-*bis*-(methylsulfonyl)pyrazine **9a**

| Entry | Bis-sulfone | Nucleophile | Product | Yield (%) |
|---|---|---|---|---|
| 1 | **9a** |  |  **10** | 90 |
| 2 | **9a** |  |  **11** | 100[a] |
| 3 | **9a** |  |  **12** | 89[b] |
| 4 | **9a** |  |  **13** | 88[a] |
| 5 | **9a** |  |  **14** | 69[c] |
| 6 | **9a** |  |  **15** | 37 |
| 7 | **9a** |  |  **16** | 34 |
| 8 | **9a** | NaOEt |  **17** | 84[d] |
| 9 | **9a** |  |  **18** | 86[e] |

[a] 2.5 equiv of the nucleophile were used.
[b] 1.0 equiv of the nucleophile was used.
[c] 1.0 equiv of the nucleophile was used and a mixture of **14**/**13** was isolated in 7:3 ratio.
[d] Refluxed in THF for 3 h with 2.2 equiv of NaOEt.
[e] Refluxed in THF overnight with 2.2 equiv of the nucleophile generated by treating malonate with NaH.

**Table 2**
$S_NAr$ reactions of 2,5-bis-*t*-butylsulfonylpyrazines (**9b**)

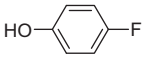
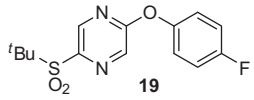
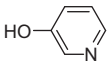
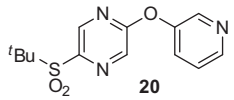
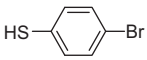
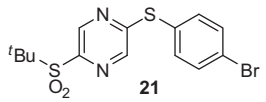
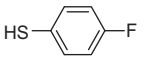
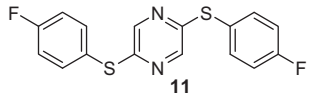
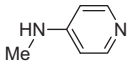
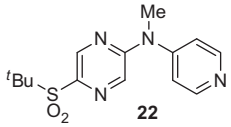
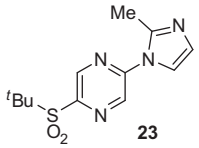
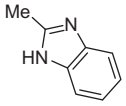
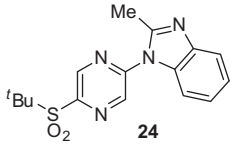
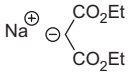
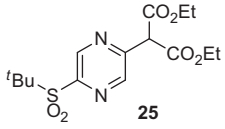
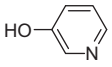
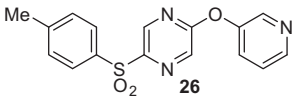
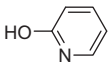
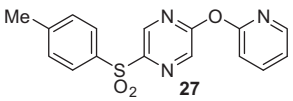
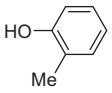
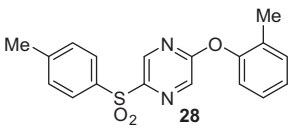
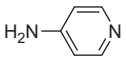
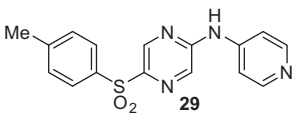
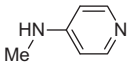
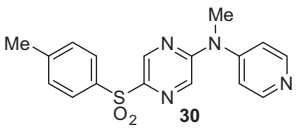
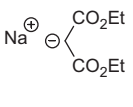
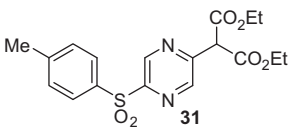
| Entry | Bis-sulfone | Nucleophile | Product | Yield (%) |
|---|---|---|---|---|
| 1 | **9b** |  |  **19** | 72 |
| 2 | **9b** |  |  **20** | 96 |
| 3 | **9b** |  |  **21** | 79 |
| 4 | **9b** |  |  **11** | 58[a] |

**Table 2** (*continued*)

| Entry | Bis-sulfone | Nucleophile | Product | Yield (%) |
|---|---|---|---|---|
| 5 | **9b** |  |  **22** | 23 |
| 6 | **9b** |  |  **23** | 81 |
| 7 | **9b** |  |  **24** | 65 |
| 8 | **9b** |  |  **25** | 86[b] |

[a] 2.2 equiv of the nucleophile were used.
[b] Refluxed overnight in THF with 2.2 equiv of the nucleophile generated by treating malonate with NaH.

**Table 3**
$S_NAr$ reactions of 2,5-bis-arylsulfonylpyrazines (**9c**)

| Entry | Bis-sulfone | Nucleophile | Product | Yield (%) |
|---|---|---|---|---|
| 1 | **9c** |  |  **26** | 93 |
| 2 | **9c** |  |  **27** | 67 |
| 3 | **9c** |  |  **28** | 99 |
| 4 | **9c** |  |  **29** | 30 |
| 5 | **9c** |  |  **30** | 34 |
| 6 | **9c** |  |  **31** | 89[a] |

[a] Refluxed overnight in THF with 2.2 equiv of the nucleophile generated by treating malonate with NaH.

nucleophile is the most reactive toward the replacement of *t*-butylsulfone, followed by phenolic oxygen, selected heterocyclic ring nitrogen, and amine nitrogen. When 1 equiv of 4-bromothiol was used (entry 3), mono-$S_NAr$ product **21** was the sole product generated in good yields. On the other hand, when 2.2 equiv of a 4-fluorobenzenethiol nucleophile were used, the bis-sulfide product **11** was isolated exclusively under the reaction conditions. In contrast, when 2.5 equiv of 4-fluorophenol were employed (entry 1), only mono-$S_NAr$ product **19** was produced due to the deactivation of the pyrazine ring as discussed above. Amine nitrogen showed limited reactivity toward this type of reaction. While **9b** was treated with *N*-methylpyridin-4-amine (entry 5), the desired mono-

$S_NAr$ product **22** was produced in 23% yield, we were unable to perform the similar transformation with aliphatic amines. Heterocyclic ring nitrogen can also be used as nucleophiles for this reaction. Both 2-methylimidazole (entry 6) and 2-methyl-1*H*-benzo[*d*]imidazole (entry 7) react readily with **9b** to provide only the mono-$S_NAr$ products **23** and **24** in good to excellent yields. When sodium malonate (entry 8) was prepared by the treatment of diethyl malonate with 1 equiv of NaH, 2-(5-(*t*-butylsulfonyl)pyrazin-2-yl)malonate (**25**) was isolated as the major product in 86% yield even when 2 equiv of nucleophile was employed.

We further investigated the *aryl*sulfonyl-pyrazines using 2,5-bis-(tolylsulfonyl)-pyrazine (**9c**) as an example. As shown in Scheme 5, double $S_NAr$ displacement of 2,5-bis-bromopyrazine (**7**) gave di-sulfide **8c**. Same oxidation procedure using hydrogen peroxide in glacial acetic acid produced bis-sulfone **9c**. We also attempted to prepare **9c** in one step by treating 2,5-bisbromopyrazine (**7**) with 2 equiv of sodium sulfinate with no success.[12]

With substrate **9c** in hand, its $S_NAr$ reactions with several different nucleophiles were explored. Reaction of 2,5-ditosylsulfonylpyrazine (**9c**) with pyridin-3-ol under typical conditions afforded 2-(pyridin-3-yloxy)-5-tosylsulfonylpyrazine (**26**) in excellent yield (Table 3, entry 1), while a much lower yield of 2-(pyridin-2-yloxy)-5-tosylsulfonylpyrazine (**27**) was obtained with pyridin-2-ol (entry 2). The lower yield resulted from the formation of 2,5-bis(pyridin-2-yloxy)pyrazine (structure not shown) as a major side product. In addition to pyridinols, we also evaluated *o*-cresol, a relatively sterically hindered phenol. This phenol (entry 3) underwent smooth mono-$S_NAr$ substitution to furnish 2-(*o*-tolyloxy)-5-tosylsulfonylpyrazine (**28**) in nearly quantitative yield. This methodology has also been extended to aminopyridines with limited success. In general, multiple substitution products from aminopyridines were observed in the crude reaction mixture as shown by LC–MS analysis, thus resulting in poor yields. For example, both pyridin-4-amine (entry 4) and *N*-methylpyridin-4-amine (entry 5) furnished the desired mono-substituted products **29** and **30** in roughly 30% yield. When pyridin-2-amine was utilized, only a trace amount of the desired mono-substituted product was formed. As aminopyridines are common building blocks for medicinal chemistry research, future work will be directed toward improving the efficiency of the reactions with 2,5-ditosylsulfonylpyrazine involving aminopyridines. When sodium malonate was prepared by the treatment of diethyl malonate with 1 equiv of NaH (entry 6), 2-(5-(tolylsulfonyl)pyrazin-2-yl)malonate (**31**) was isolated as the predominant product in 89% yield even when 2 equiv of nucleophile was employed.

In summary, we have prepared the previously unknown 2,5-bis-(sulfonyl)-pyrazines including 2,5-bis-(methysulfonyl)-pyrazine (**9a**), 2,5-bis(*t*-butylsulfonyl)-pyrazine (**9b**), and 2,5-bis(tolylsulfonyl)pyrazine (**9c**). The respective $S_NAr$ reactions of these have been explored with a variety of nucleophiles. When 2 equiv of thiols or thiophenols were employed as the nucleophiles, bis-thiopyrazines were obtained exclusively. However, phenols or alkoxides only gave rise to the corresponding mono-substituted aryloxy- or alkoxy-sulfonylpyrazines in excellent yields because the pyrazine is deactivated by the oxygen atom. A carbon nucleophile prepared by treating malonate with NaH also produced the corresponding mono-sulfonylpyrazines even though 2 equiv of the nucleophile was used. Finally, the $S_NAr$ reaction of aliphatic amines and anilines with 2,5-bis-(sulfonyl)pyrazines provided the mono-anilino-sulfonylpyrazines in poor to moderate yields.

## Supplementary data

Supplementary data (full experimental detail, as well as characterization of all compounds) associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2013.01.106.

## References and notes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9. *Typical experimental procedure*: To a suspension of 2,5-bis(methylsulfonyl)-pyrazine (**9a**, 500 mg, 2.12 mmol) in acetonitrile (5 mL) was added *para*-fluorophenol (593 mg, 5.29 mmol, 2.5 equiv) and $K_2CO_3$ (877 mg, 6.35 mmol, 3 equiv) The resulting suspension was refluxed for 2 h and cooled to rt. The suspension was filtered, the solvent was removed in vacuo and the residue was purified using a column eluting with 30–50% EtOAc in hexanes to give the desired product **10** as a white and highly crystalline solid (512 mg, 90%). $R_f$ = 0.51 (1:1 hexanes/EtOAc); $^1$H NMR (300 MHz, $CDCl_3$) $\delta$: 8.69 (s, 1H), 8.44 (s, 1H), 7.09 (m, 4H), 3.15 (s, 3H); $^{19}$F NMR (282 MHz, $CDCl_3$) $\delta$: 116.2; $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$: 165.6, 164.0 (d), 148.6, 141.4 (d), 137.7 (d), 121.7 (d), 117.4 (d); MS (ESI+) *m*/*z* 269.11 (M+1).
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