

含 6-氟喹唑啉片段的新型 1,3,4-噁(噻)二唑类衍生物的  
合成及抗菌活性研究石 军 罗 娜 丁慕晗 李传会 万苏然 李培甲  
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**摘要** 为寻找高效农用抗菌先导化合物,通过活性亚结构拼接法设计合成了 50 个含 6-氟喹唑啉片段的新型 1,3,4-噁(噻)二唑类衍生物 **6a~6y** 和 **8a~8y**,其结构经  $^1\text{H}$  NMR、 $^{13}\text{C}$  NMR 和 HRMS 手段进行了表征,且化合物 **6i** 和 **8x** 的结构最终由 X 射线单晶衍射法加以确认。初步抗菌测试表明,部分化合物表现出较好的体外抗真菌活性。在 50  $\mu\text{g/mL}$  浓度下,化合物 **6b**、**6d**、**6t**、**6v** 和 **6x** 对小麦赤霉病菌的抑制率分别为 58%、58%、55%、63%和 60%,化合物 **6v** 和 **8v** 对苹果腐烂病菌的抑制率分别为 71%和 64%,化合物 **6v** 对油菜炭疽病菌的抑制率为 72%,它们均优于对照药剂噁霉灵(分别为 51%、61%和 70%)。此外,部分化合物在 100  $\mu\text{g/mL}$  浓度下也表现出一定的体外抗细菌活性。

**关键词** 1,3,4-噁二唑; 1,3,4-噻二唑; 6-氟喹唑啉; 合成; 抗菌活性

Synthesis and Antimicrobial Activities of Novel 1,3,4-Oxa(Thia)-  
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**Abstract** To search efficient agricultural antimicrobial lead compounds, fifty 1,3,4-oxa(thia)diazole derivatives **6a~6y** and **8a~8y** containing 6-fluoroquinazoline moiety were designed, synthesized and evaluated for their antimicrobial activities, based on the method of the splicing of bioactive substructures. The structures of target compounds were fully characterized by  $^1\text{H}$  NMR,  $^{13}\text{C}$  NMR, and HRMS spectra, and two compounds **6i** and **8x** were further confirmed via single crystal X-ray diffraction analysis. The preliminary bioassays revealed that some compounds exhibited good antifungal activity *in vitro*. For example, compounds **6b**, **6d**, **6t**, **6v** and **6x** were found to have the inhibition rates of 58%, 58%, 55%, 63% and 60% against *Gibberella zeae* at 50  $\mu\text{g/mL}$ , respectively. Additionally, compounds **6v** and **8v** displayed the inhibition efficacies of 71% and 64% against *Cytospora mandshurica* at 50  $\mu\text{g/mL}$ , respectively. Moreover, compound **6v** demonstrated an inhibition rate of 72% against *Colletotrichum gloeosporioides* at 50  $\mu\text{g/mL}$ . The above activities were all better than that of control agent Hymexazol (51%, 61%, and 70%, respectively). Finally, some compounds also showed certain inhibition potencies *in vitro* against tested bacteria at 100  $\mu\text{g/mL}$ .

**Keywords** 1,3,4-oxadiazole; 1,3,4-thiadiazole; 6-fluoroquinazoline; synthesis; antimicrobial activity

植物病原菌因其对农业生产的巨大危害而受到全球农业化学家们的广泛关注,比如植物病原真菌能寄生

在多种重要农作物上,从而诱发多种作物疾病,每年都给世界农业生产造成巨大经济损失<sup>[1-3]</sup>。此外,植物病原

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Received July 29, 2020; revised August 11, 2020; published online September 15, 2020.

Supported by the Natural Science Foundation of Guizhou Province (No. 20201Z025), the Young Top-Notch Talent Support Program of Guizhou Provincial Education Department (No. 2018038) and the Guizhou Provincial High-Level Overseas Talents Innovation and Entrepreneurship Program (No. 201809).  
贵州省自然科学基金(No. 20201Z025)、贵州省教育厅科技拔尖人才支持计划(No. 2018038)和贵州省高层次留学人才创新创业(No. 201809)资助项目。

细菌目前也成为农业生产的一种重要病害<sup>[4]</sup>. 与其它防控方法相比, 化学防治具有高效、低成本和方便施用等显著优势. 然而, 由于现有农用抗菌剂的大量滥用而导致的病原菌耐药性不断增加、药剂防控效果下降和环境污染等系列问题<sup>[5-6]</sup>, 因此寻找高效、低毒且具有新颖化学结构的杀菌剂已成为当前农药化学领域的一个研究热点.

含氮杂环化合物因其多样化的结构形式和广谱的生物活性, 成为新农药创制的研究热点<sup>[7-8]</sup>. 其中, 1,3,4-噁二唑和 1,3,4-噻二唑类衍生物都是重要的五元杂环化合物, 它们在医药和农药等领域有着广泛应用. 已商品化的 1,3,4-噁(噻)二唑类药物有抗 HIV(人类免疫缺陷病毒)药雷特格韦(Raltegravir)、抗高血压药疏达唑嗪(Tiodazosin)、农用细菌性杀菌剂叶枯唑(Bismethiazol)和兽用抗菌剂磺胺甲噁二唑(Sulfamethizole)(图 1). 此外, 研究发现 1,3,4-噁(噻)二唑类衍生物也具有其它生物活性, 如抗菌<sup>[9-12]</sup>、除草<sup>[13-14]</sup>、杀(线)虫<sup>[15-17]</sup>、抗肿

瘤<sup>[18]</sup>和抗糖尿病<sup>[19]</sup>等. 另一方面, 6-氟喹唑啉类衍生物表现出多种生物和药理活性, 如抗细菌<sup>[9]</sup>、抗真菌<sup>[20]</sup>、抗 TMV(烟草花叶病毒)<sup>[21]</sup>、抗 HBV(乙型肝炎病毒)<sup>[22]</sup>和抗惊厥<sup>[23]</sup>等. 再次, 以哌啶环为中间连接基的结构单元经常出现在药物分子中<sup>[24]</sup>, 比如多巴胺受体拮抗剂氯波必利(Clebopride)、麻醉止痛药芬太尼(Fentanyl)和抗过敏药阿司咪唑(Astemizole)等.

活性亚结构拼接法有助于发挥不同药效团之间的协同效应, 是发现高活性农药分子一种有效方法<sup>[15,25]</sup>. 为寻找高效农用抗菌先导化合物, 本文以 5-氟氨基苯甲酸为起始原料, 基于活性亚结构拼接原理将 6-氟喹唑啉片段通过哌啶环引入到 1,3,4-噁(噻)二唑骨架中, 设计合成了 50 个新型 1,3,4-噁(噻)二唑类衍生物(图 2), 测试了它们对常见的植物病原真菌和植物病原细菌的体外抑制活性, 并对目标化合物的抗真菌活性与其分子结构之间的相互关系进行了初步探讨.

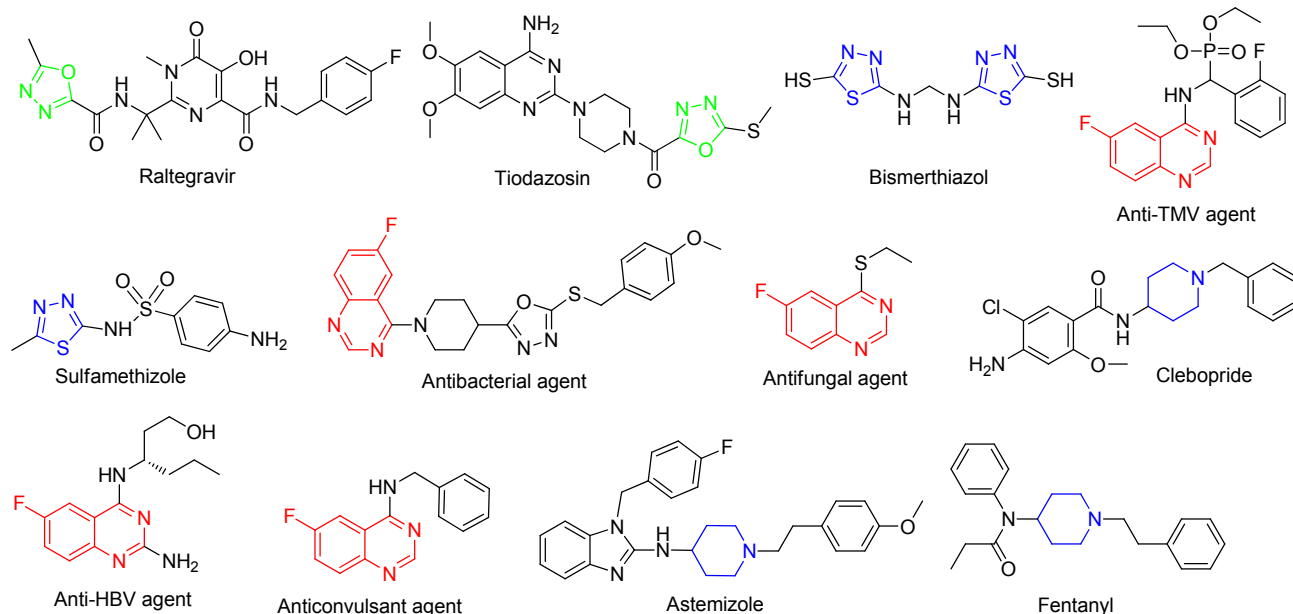


图 1 部分含 1,3,4-噁二唑、1,3,4-噻二唑、6-氟喹唑啉或哌啶桥的生物活性分子

Figure 1 Some bioactive molecules containing the 1,3,4-oxadiazole, 1,3,4-thiadiazole, 6-fluoroquinazoline moiety or piperidiny linker

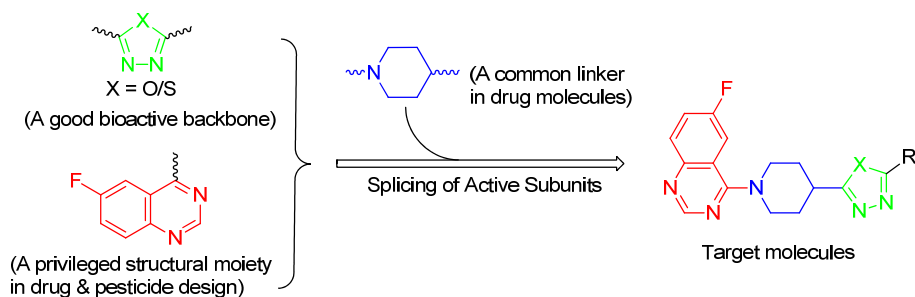


图 2 目标化合物的设计策略

Figure 2 Design strategy for the target compounds in this work

## 1 结果与讨论

### 1.1 目标化合物的合成

目标化合物的合成路线见 Scheme 1. 首先, 哌啶甲酰肼 **4**<sup>[9]</sup> 与不同芳醛在乙醇中进行缩合反应得到相应的哌啶甲酰腙 **5**, 该中间体未经分离直接进行下一步反应. 在碱性条件下, 酰腙 **5** 在碘单质作用下发生分子内氧化关环反应, 得到目标化合物 **6a~6y**. 另外, 以哌啶甲酰肼 **4** 和不同芳酰氯在二氯甲烷溶液中进行缩合反应, 得到中间体双酰肼 **7**, 然后 **7** 与五硫化二磷在回流的二甲苯中发生关环反应得到目标化合物 **8a~8y**.

### 1.2 目标化合物的波谱数据解析

以化合物 **6i** 为例, 对其核磁共振氢谱和碳谱数据进行解析. 在 <sup>1</sup>H NMR 谱中, **6i** 的喹啉环 2 位 CH 在  $\delta$  8.67 处以单峰形式出现; 在  $\delta$  8.03 和 7.68 处两组双重峰归于与噁二唑相连的对氯苯环上的质子; 喹啉环 8 位 CH 与邻近的 7 位 CH 和 6 位氟原子之间存在偶合裂分, 故在  $\delta$  7.92 处以一组 dd 峰形式出现; 喹啉环 5 位 CH 由于同样原因, 在  $\delta$  7.78 处也以 dd 峰形成出现; 喹啉环 7 位 CH 在  $\delta$  7.76~7.72 处以多重峰出现. 此外, 哌啶环上的次甲基 CH 在  $\delta$  3.53~3.47 以多重峰形式存在. 在 <sup>13</sup>C NMR 谱中, 喹啉环 4 位碳处于最低场  $\delta$  168.8; 喹啉环 6 位碳与相连的氟存在偶合裂分, 在  $\delta$  158.6 以双重峰出现 ( $J_{C-F}$  = 244.0 Hz); 哌啶环上的三组脂肪碳  $\delta$  分别位于 48.4、32.5 和 28.6 处. 在 HRMS-ESI 谱中,

化合物 **6i** 在 410.1170 处出现归属于  $[M+H]^+$  的准分子离子峰, 这也进一步证实其分子结构.

### 1.3 化合物的单晶结构

为最终确认目标化合物的结构, 采用溶剂缓慢挥发法在 DMF/EtOH ( $V/V=4/1$ ) 的混合溶剂中培养了化合物 **6i** 和 **8x** 的单晶(图 3 和 4), 这与 Scheme 1 中描述的结构式一致.

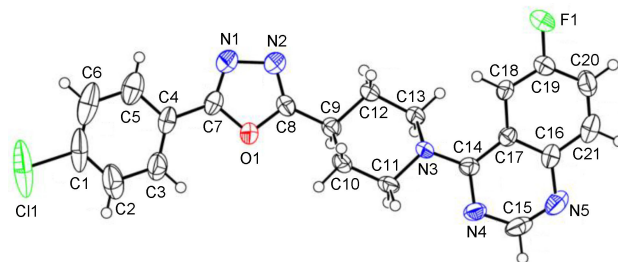


图 3 化合物 **6i** 的晶体结构(CCDC 1916791)

Figure 3 Crystal structure of compound **6i** (CCDC 1916791)

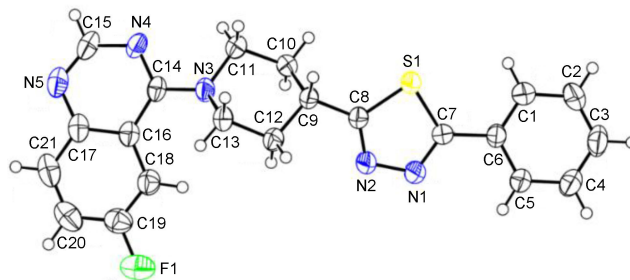
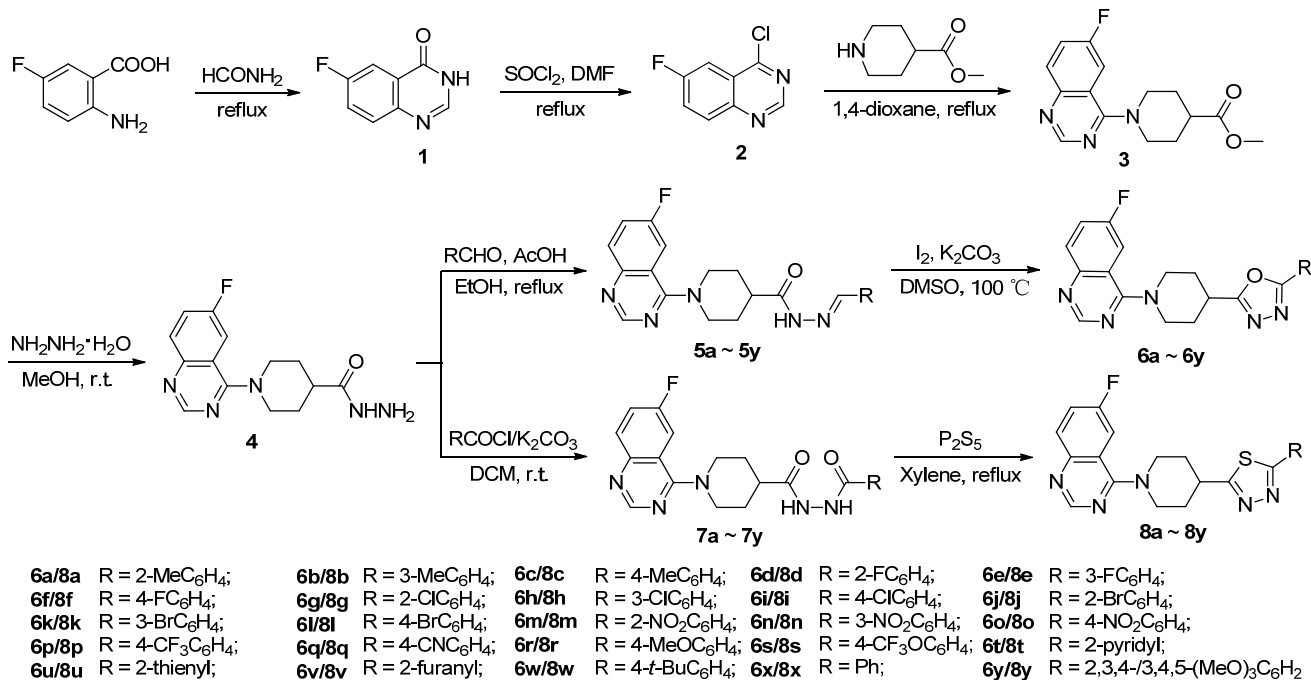


图 4 化合物 **8x** 的晶体结构(CCDC 1916823)

Figure 4 Crystal structure of compound **8x** (CCDC 1916823)



图式 1 目标化合物 **6a~6y** 和 **8a~8y** 的合成路线

Scheme 1 Synthetic route of target compounds **6a~6y** and **8a~8y**

## 1.4 目标化合物的抑菌活性测试结果

## 1.4.1 抗真菌活性结果

采用菌丝生长速率法<sup>[2,25]</sup>, 测试了目标化合物 **6a**~**6y** 和 **8a**~**8y** 在体外对小麦赤霉病菌(*Gibberella zeae*)、油菜炭疽病菌(*Colletotrichum gloeosporioides*)和苹果腐烂病菌(*Cytospora mandshurica*)三种病原真菌的抑制活性, 同时以商品化杀菌剂噁霉灵(Hymexazol)为阳性对照. 从表 1 可知, 部分化合物对受试真菌表现出较好抑制活性. 在 50  $\mu\text{g/mL}$  浓度下, 化合物 **6b**、**6d**、**6t**、**6v**、**6x** 和 **8v** 对小麦赤霉菌的抑制率分别为 58%、58%、55%、63%、60%和 54%, 优于噁霉灵(51%); 化合物 **6v** 和 **8v** 在该浓度下对苹果腐烂菌的抑制率分别为 71% 和 64%, 高于噁霉灵(61%); 化合物 **6v** 对油菜炭疽病菌的抑制率

为 72%, 与噁霉灵相当(70%).

简单的构效关系分析表明: 含 6-氟喹啉片段的 1,3,4-噁二唑衍生物的抗真菌活性整体优于对应的 1,3,4-噁二唑类衍生物; 对于 1,3,4-噁二唑类衍生物而言, 当其 5 位取代基为邻氟苯基(2-FC<sub>6</sub>H<sub>4</sub>)时表现出最佳抗真菌活性, 明显高于其它卤代(Cl/Br)苯基, 这可能与含氟化合物特有的“氟效应”有关; 当 R 为芳杂环取代基时, 含呋喃环结构的化合物 **6v** 和 **8v** 活性较含吡啶和噻吩环的化合物高, 这表明呋喃环的存在有利于目标分子的抗真菌活性; 整体而言, 化合物 **6d**、**6v** 和 **8v** 对三种真菌都表现出较好的抑制活性(>50%). 本文分子设计是基于活性亚结构拼接原理, 没有涉及靶向性分子设计, 这可能是导致目标化合物杀菌活性并不太理想的原因.

表 1 目标化合物 **6a**~**6y** 和 **8a**~**8y** 在 50  $\mu\text{g/mL}$  浓度下的抗真菌活性  
Table 1 Antifungal activities of target compounds **6a**~**6y** and **8a**~**8y** at 50  $\mu\text{g/mL}$

| Compd.                 | Inhibition rate <sup>a</sup> /% |                 |                 | Compd.    | Inhibition rate <sup>a</sup> /% |                 |                 |
|------------------------|---------------------------------|-----------------|-----------------|-----------|---------------------------------|-----------------|-----------------|
|                        | GZ <sup>c</sup>                 | CG <sup>c</sup> | CM <sup>c</sup> |           | GZ <sup>c</sup>                 | CG <sup>c</sup> | CM <sup>c</sup> |
| <b>6a</b>              | 40 $\pm$ 2                      | 20 $\pm$ 1      | 17 $\pm$ 2      | <b>8a</b> | 45 $\pm$ 1                      | 47 $\pm$ 1      | 50 $\pm$ 1      |
| <b>6b</b>              | 58 $\pm$ 2                      | 42 $\pm$ 0      | 45 $\pm$ 0      | <b>8b</b> | 31 $\pm$ 1                      | 34 $\pm$ 1      | 40 $\pm$ 1      |
| <b>6c</b>              | 11 $\pm$ 0                      | 16 $\pm$ 2      | 15 $\pm$ 3      | <b>8c</b> | 30 $\pm$ 2                      | 32 $\pm$ 2      | 33 $\pm$ 2      |
| <b>6d</b>              | 58 $\pm$ 2                      | 52 $\pm$ 1      | 55 $\pm$ 2      | <b>8d</b> | 26 $\pm$ 1                      | 29 $\pm$ 2      | 33 $\pm$ 2      |
| <b>6e</b>              | 40 $\pm$ 2                      | 13 $\pm$ 1      | 15 $\pm$ 3      | <b>8e</b> | 32 $\pm$ 1                      | 7 $\pm$ 1       | 18 $\pm$ 2      |
| <b>6f</b>              | 43 $\pm$ 2                      | 11 $\pm$ 1      | 18 $\pm$ 1      | <b>8f</b> | 25 $\pm$ 1                      | 16 $\pm$ 2      | 18 $\pm$ 2      |
| <b>6g</b>              | 22 $\pm$ 1                      | 14 $\pm$ 2      | 16 $\pm$ 0      | <b>8g</b> | 19 $\pm$ 1                      | 32 $\pm$ 1      | 34 $\pm$ 2      |
| <b>6h</b>              | 37 $\pm$ 2                      | 13 $\pm$ 1      | 17 $\pm$ 3      | <b>8h</b> | 28 $\pm$ 1                      | 23 $\pm$ 3      | 22 $\pm$ 3      |
| <b>6i</b>              | 52 $\pm$ 1                      | 29 $\pm$ 2      | 30 $\pm$ 3      | <b>8i</b> | 30 $\pm$ 1                      | 19 $\pm$ 3      | 18 $\pm$ 1      |
| <b>6j</b>              | 9 $\pm$ 1                       | 22 $\pm$ 3      | 13 $\pm$ 2      | <b>8j</b> | 28 $\pm$ 1                      | 28 $\pm$ 2      | 27 $\pm$ 1      |
| <b>6k</b>              | 34 $\pm$ 3                      | 22 $\pm$ 1      | 25 $\pm$ 2      | <b>8k</b> | 0                               | 9 $\pm$ 2       | 9 $\pm$ 2       |
| <b>6l</b>              | 38 $\pm$ 1                      | 26 $\pm$ 3      | 26 $\pm$ 2      | <b>8l</b> | 21 $\pm$ 1                      | 23 $\pm$ 3      | 21 $\pm$ 2      |
| <b>6m</b>              | 0                               | 0               | 8 $\pm$ 3       | <b>8m</b> | 13 $\pm$ 3                      | 21 $\pm$ 1      | 17 $\pm$ 1      |
| <b>6n</b>              | 43 $\pm$ 3                      | 24 $\pm$ 1      | 25 $\pm$ 2      | <b>8n</b> | 16 $\pm$ 1                      | 15 $\pm$ 3      | 22 $\pm$ 3      |
| <b>6o</b>              | 37 $\pm$ 2                      | 13 $\pm$ 2      | 8 $\pm$ 1       | <b>8o</b> | 0                               | 15 $\pm$ 1      | 22 $\pm$ 3      |
| <b>6p</b>              | 31 $\pm$ 1                      | 6 $\pm$ 2       | 10 $\pm$ 2      | <b>8p</b> | 0                               | 0               | 0               |
| <b>6q</b>              | 43 $\pm$ 1                      | 25 $\pm$ 2      | 29 $\pm$ 3      | <b>8q</b> | 31 $\pm$ 1                      | 7 $\pm$ 2       | 10 $\pm$ 1      |
| <b>6r</b>              | 34 $\pm$ 1                      | 0               | 9 $\pm$ 3       | <b>8r</b> | 12 $\pm$ 1                      | 16 $\pm$ 3      | 15 $\pm$ 3      |
| <b>6s</b>              | 43 $\pm$ 1                      | 21 $\pm$ 0      | 26 $\pm$ 1      | <b>8s</b> | 20 $\pm$ 1                      | 7 $\pm$ 2       | 9 $\pm$ 2       |
| <b>6t</b>              | 55 $\pm$ 3                      | 43 $\pm$ 2      | 47 $\pm$ 1      | <b>8t</b> | 46 $\pm$ 1                      | 36 $\pm$ 2      | 44 $\pm$ 1      |
| <b>6u</b>              | 51 $\pm$ 2                      | 21 $\pm$ 1      | 19 $\pm$ 2      | <b>8u</b> | 11 $\pm$ 1                      | 21 $\pm$ 2      | 25 $\pm$ 2      |
| <b>6v</b>              | 63 $\pm$ 1                      | 72 $\pm$ 1      | 71 $\pm$ 1      | <b>8v</b> | 54 $\pm$ 1                      | 50 $\pm$ 2      | 64 $\pm$ 2      |
| <b>6w</b>              | 16 $\pm$ 2                      | 13 $\pm$ 2      | 13 $\pm$ 2      | <b>8w</b> | 17 $\pm$ 3                      | 22 $\pm$ 2      | 14 $\pm$ 3      |
| <b>6x</b>              | 60 $\pm$ 2                      | 33 $\pm$ 2      | 45 $\pm$ 0      | <b>8x</b> | 16 $\pm$ 1                      | 15 $\pm$ 2      | 21 $\pm$ 3      |
| <b>6y</b>              | 16 $\pm$ 3                      | 11 $\pm$ 2      | 31 $\pm$ 4      | <b>8y</b> | 26 $\pm$ 1                      | 23 $\pm$ 2      | 24 $\pm$ 2      |
| Hymexazol <sup>b</sup> | 51 $\pm$ 1                      | 70 $\pm$ 1      | 61 $\pm$ 1      |           |                                 |                 |                 |

<sup>a</sup> The average of three trials. <sup>b</sup> The commercial agrofungicide hymexazol (99%) was used as a positive control. <sup>c</sup> GZ=*Gibberella zeae*; CG=*Colletotrichum gloeosporioides*; CM=*Cytospora mandshurica*.

## 1.4.2 抗细菌活性结果

采用浊度法<sup>[5,25]</sup>, 以水稻白叶枯病菌(*Xanthomonas oryzae* pv. *oryzae*, Xoo)、柑橘溃疡病菌(*Xanthomonas axonopodis* pv. *citri*, Xac)和烟草青枯病菌(*Ralstonia solanacearum*, Rs)为测试对象, 同时以商品化药剂叶枯唑(Bismethiazol)和噻菌铜(Thiodiazole copper)为阳性对照

药剂, 测定了目标化合物 **6a**~**6y** 和 **8a**~**8y** 的体外抗细菌活性. 由表 2 可知, 大部分目标化合物对上述三种病原细菌均表现出一定的抑制作用. 其中, 在 100  $\mu\text{g/mL}$  浓度下, 化合物 **8j** 和 **8x** 对 Rs 的抑制率分别为 66%和 56%, 高于叶枯唑(50%)和噻菌铜(43%); 相同浓度下化合物 **8b** 和 **8x** 对 Xac 的抑制率分别为 54%和 56%, 与对

表 2 目标化合物 6a~6y 和 8a~8y 对 *Xoo*、*Xac* 和 *Rs* 的抗菌活性(抑制率/%)<sup>a</sup>Table 2 Antibacterial activities (inhibition rate/%) of target compounds 6a~6y and 8a~8y against *Xac*, *Xoo* and *Rs*

| Compd.           | <i>Xanthomonas axonopodis</i> pv. <i>citri</i> |                     | <i>Xanthomonas oryzae</i> pv. <i>oryzae</i> |                     | <i>Ralstonia solanacearum</i> |                     |
|------------------|------------------------------------------------|---------------------|---------------------------------------------|---------------------|-------------------------------|---------------------|
|                  | 100 $\mu\text{g/mL}$                           | 50 $\mu\text{g/mL}$ | 100 $\mu\text{g/mL}$                        | 50 $\mu\text{g/mL}$ | 100 $\mu\text{g/mL}$          | 50 $\mu\text{g/mL}$ |
| 6a               | 38 $\pm$ 4                                     | 33 $\pm$ 2          | 32 $\pm$ 3                                  | 18 $\pm$ 2          | 9 $\pm$ 3                     | 5 $\pm$ 3           |
| 6b               | 32 $\pm$ 3                                     | 16 $\pm$ 3          | 27 $\pm$ 3                                  | 22 $\pm$ 5          | 21 $\pm$ 2                    | 14 $\pm$ 3          |
| 6c               | 40 $\pm$ 3                                     | 30 $\pm$ 2          | 43 $\pm$ 3                                  | 36 $\pm$ 1          | 20 $\pm$ 5                    | 13 $\pm$ 4          |
| 6d               | 38 $\pm$ 3                                     | 28 $\pm$ 2          | 31 $\pm$ 3                                  | 30 $\pm$ 2          | 14 $\pm$ 3                    | 12 $\pm$ 5          |
| 6e               | 31 $\pm$ 4                                     | 27 $\pm$ 4          | 29 $\pm$ 3                                  | 15 $\pm$ 0          | 18 $\pm$ 2                    | 17 $\pm$ 1          |
| 6f               | 41 $\pm$ 4                                     | 25 $\pm$ 5          | 27 $\pm$ 4                                  | 24 $\pm$ 4          | 17 $\pm$ 1                    | 6 $\pm$ 3           |
| 6g               | 39 $\pm$ 3                                     | 20 $\pm$ 2          | 35 $\pm$ 1                                  | 17 $\pm$ 3          | 21 $\pm$ 4                    | 16 $\pm$ 2          |
| 6h               | 39 $\pm$ 4                                     | 29 $\pm$ 2          | 27 $\pm$ 1                                  | 21 $\pm$ 4          | 28 $\pm$ 0                    | 17 $\pm$ 4          |
| 6i               | 32 $\pm$ 2                                     | 30 $\pm$ 4          | 33 $\pm$ 6                                  | 23 $\pm$ 5          | 33 $\pm$ 2                    | 24 $\pm$ 3          |
| 6j               | 31 $\pm$ 5                                     | 26 $\pm$ 5          | 37 $\pm$ 3                                  | 14 $\pm$ 2          | 18 $\pm$ 3                    | 15 $\pm$ 2          |
| 6k               | 35 $\pm$ 5                                     | 24 $\pm$ 4          | 18 $\pm$ 5                                  | 13 $\pm$ 2          | 27 $\pm$ 3                    | 13 $\pm$ 4          |
| 6l               | 38 $\pm$ 3                                     | 27 $\pm$ 3          | 26 $\pm$ 3                                  | 19 $\pm$ 3          | 47 $\pm$ 2                    | 23 $\pm$ 3          |
| 6m               | 35 $\pm$ 3                                     | 20 $\pm$ 5          | 32 $\pm$ 5                                  | 29 $\pm$ 2          | 17 $\pm$ 2                    | 16 $\pm$ 2          |
| 6n               | 36 $\pm$ 3                                     | 26 $\pm$ 5          | 33 $\pm$ 3                                  | 21 $\pm$ 3          | 25 $\pm$ 2                    | 20 $\pm$ 3          |
| 6o               | 38 $\pm$ 1                                     | 27 $\pm$ 3          | 26 $\pm$ 2                                  | 11 $\pm$ 4          | 29 $\pm$ 3                    | 9 $\pm$ 4           |
| 6p               | 39 $\pm$ 1                                     | 30 $\pm$ 3          | 20 $\pm$ 4                                  | 17 $\pm$ 4          | 19 $\pm$ 2                    | 13 $\pm$ 5          |
| 6q               | 31 $\pm$ 6                                     | 21 $\pm$ 2          | 16 $\pm$ 5                                  | 7 $\pm$ 1           | 15 $\pm$ 4                    | 9 $\pm$ 3           |
| 6r               | 41 $\pm$ 3                                     | 28 $\pm$ 3          | 21 $\pm$ 3                                  | 14 $\pm$ 1          | 26 $\pm$ 2                    | 21 $\pm$ 3          |
| 6s               | 50 $\pm$ 4                                     | 37 $\pm$ 2          | 33 $\pm$ 2                                  | 30 $\pm$ 5          | 17 $\pm$ 3                    | 13 $\pm$ 3          |
| 6t               | 45 $\pm$ 3                                     | 32 $\pm$ 3          | 37 $\pm$ 5                                  | 20 $\pm$ 3          | 26 $\pm$ 5                    | 18 $\pm$ 3          |
| 6u               | 40 $\pm$ 2                                     | 30 $\pm$ 2          | 40 $\pm$ 4                                  | 36 $\pm$ 7          | 33 $\pm$ 3                    | 29 $\pm$ 3          |
| 6v               | 44 $\pm$ 4                                     | 34 $\pm$ 2          | 33 $\pm$ 1                                  | 18 $\pm$ 1          | 34 $\pm$ 3                    | 31 $\pm$ 5          |
| 6w               | 37 $\pm$ 4                                     | 28 $\pm$ 5          | 45 $\pm$ 5                                  | 27 $\pm$ 2          | 35 $\pm$ 3                    | 33 $\pm$ 3          |
| 6x               | 41 $\pm$ 3                                     | 33 $\pm$ 3          | 49 $\pm$ 4                                  | 22 $\pm$ 5          | 30 $\pm$ 2                    | 16 $\pm$ 2          |
| 6y               | 29 $\pm$ 4                                     | 21 $\pm$ 4          | 57 $\pm$ 2                                  | 47 $\pm$ 2          | 48 $\pm$ 4                    | 35 $\pm$ 3          |
| 8a               | 44 $\pm$ 5                                     | 27 $\pm$ 3          | 30 $\pm$ 6                                  | 27 $\pm$ 3          | 25 $\pm$ 4                    | 23 $\pm$ 3          |
| 8b               | 54 $\pm$ 3                                     | 32 $\pm$ 2          | 32 $\pm$ 4                                  | 22 $\pm$ 2          | 34 $\pm$ 3                    | 28 $\pm$ 3          |
| 8c               | 42 $\pm$ 1                                     | 35 $\pm$ 4          | 40 $\pm$ 1                                  | 35 $\pm$ 4          | 22 $\pm$ 5                    | 18 $\pm$ 4          |
| 8d               | 41 $\pm$ 4                                     | 32 $\pm$ 4          | 37 $\pm$ 1                                  | 32 $\pm$ 4          | 44 $\pm$ 2                    | 37 $\pm$ 4          |
| 8e               | 32 $\pm$ 0                                     | 29 $\pm$ 3          | 35 $\pm$ 2                                  | 29 $\pm$ 3          | 48 $\pm$ 2                    | 37 $\pm$ 1          |
| 8f               | 38 $\pm$ 2                                     | 29 $\pm$ 3          | 33 $\pm$ 5                                  | 29 $\pm$ 3          | 49 $\pm$ 2                    | 41 $\pm$ 3          |
| 8g               | 31 $\pm$ 1                                     | 26 $\pm$ 4          | 30 $\pm$ 8                                  | 26 $\pm$ 4          | 36 $\pm$ 5                    | 30 $\pm$ 4          |
| 8h               | 36 $\pm$ 4                                     | 29 $\pm$ 1          | 34 $\pm$ 3                                  | 29 $\pm$ 1          | 20 $\pm$ 4                    | 17 $\pm$ 4          |
| 8i               | 36 $\pm$ 2                                     | 31 $\pm$ 5          | 27 $\pm$ 6                                  | 31 $\pm$ 5          | 28 $\pm$ 3                    | 24 $\pm$ 1          |
| 8j               | 40 $\pm$ 3                                     | 38 $\pm$ 3          | 38 $\pm$ 8                                  | 35 $\pm$ 3          | 66 $\pm$ 1                    | 46 $\pm$ 1          |
| 8k               | 33 $\pm$ 1                                     | 30 $\pm$ 1          | 39 $\pm$ 3                                  | 32 $\pm$ 1          | 29 $\pm$ 4                    | 21 $\pm$ 4          |
| 8l               | 43 $\pm$ 2                                     | 31 $\pm$ 1          | 32 $\pm$ 8                                  | 31 $\pm$ 1          | 35 $\pm$ 3                    | 33 $\pm$ 2          |
| 8m               | 40 $\pm$ 4                                     | 28 $\pm$ 1          | 34 $\pm$ 4                                  | 28 $\pm$ 1          | 24 $\pm$ 3                    | 23 $\pm$ 3          |
| 8n               | 33 $\pm$ 3                                     | 30 $\pm$ 2          | 37 $\pm$ 3                                  | 30 $\pm$ 2          | 17 $\pm$ 4                    | 12 $\pm$ 6          |
| 8o               | 29 $\pm$ 2                                     | 20 $\pm$ 1          | 23 $\pm$ 8                                  | 20 $\pm$ 1          | 22 $\pm$ 3                    | 13 $\pm$ 3          |
| 8p               | 39 $\pm$ 4                                     | 28 $\pm$ 1          | 35 $\pm$ 8                                  | 28 $\pm$ 1          | 21 $\pm$ 4                    | 15 $\pm$ 4          |
| 8q               | 43 $\pm$ 4                                     | 30 $\pm$ 4          | 41 $\pm$ 0                                  | 30 $\pm$ 4          | 33 $\pm$ 3                    | 31 $\pm$ 2          |
| 8r               | 43 $\pm$ 3                                     | 31 $\pm$ 3          | 34 $\pm$ 5                                  | 31 $\pm$ 3          | 40 $\pm$ 4                    | 35 $\pm$ 4          |
| 8s               | 42 $\pm$ 3                                     | 39 $\pm$ 4          | 40 $\pm$ 2                                  | 32 $\pm$ 4          | 30 $\pm$ 2                    | 23 $\pm$ 7          |
| 8t               | 40 $\pm$ 4                                     | 34 $\pm$ 2          | 40 $\pm$ 3                                  | 34 $\pm$ 2          | 34 $\pm$ 2                    | 33 $\pm$ 5          |
| 8u               | 39 $\pm$ 5                                     | 31 $\pm$ 5          | 36 $\pm$ 4                                  | 31 $\pm$ 5          | 30 $\pm$ 3                    | 27 $\pm$ 3          |
| 8v               | 44 $\pm$ 3                                     | 25 $\pm$ 2          | 31 $\pm$ 3                                  | 20 $\pm$ 1          | 28 $\pm$ 2                    | 16 $\pm$ 4          |
| 8w               | 36 $\pm$ 2                                     | 29 $\pm$ 2          | 26 $\pm$ 3                                  | 21 $\pm$ 3          | 24 $\pm$ 4                    | 14 $\pm$ 2          |
| 8x               | 56 $\pm$ 3                                     | 52 $\pm$ 2          | 52 $\pm$ 3                                  | 40 $\pm$ 2          | 56 $\pm$ 3                    | 37 $\pm$ 4          |
| 8y               | 47 $\pm$ 5                                     | 35 $\pm$ 2          | 40 $\pm$ 4                                  | 35 $\pm$ 2          | 32 $\pm$ 3                    | 21 $\pm$ 1          |
| BMT <sup>b</sup> | 54 $\pm$ 1                                     | 37 $\pm$ 4          | 60 $\pm$ 2                                  | 43 $\pm$ 5          | 50 $\pm$ 4                    | 33 $\pm$ 2          |
| TDC <sup>b</sup> | NT <sup>c</sup>                                | NT <sup>c</sup>     | NT <sup>c</sup>                             | NT <sup>c</sup>     | 43 $\pm$ 3                    | 27 $\pm$ 2          |

<sup>a</sup> The average of three trials. <sup>b</sup> Commercial bactericides bismerthiazol (BMT) and thiodiazole-copper (TDC) were used as positive control agents. <sup>c</sup> NT=not tested.

照药叶枯唑相当(54%); 化合物 **6y** 对 *Xoo* 的抑制率为 57%, 与叶枯唑相近(60%)。

## 2 结论

利用活性亚单元拼接法, 经多步反应设计合成了 50 个含 6-氟喹唑啉片段的 1,3,4-噁二唑和 1,3,4-噻二唑类衍生物 **6a~6y** 和 **8a~8y**。生物活性测试实验表明, 部分化合物表现出较好的体外抗菌活性。其中, 在 50  $\mu\text{g/mL}$  浓度下, 化合物 **6b**、**6d**、**6t**、**6v** 和 **6x** 对小麦赤霉病菌的抑制率分别为 58%、58%、55%、63%和 60%, 化合物 **6v** 和 **8v** 对苹果腐烂病菌的抑制率分别为 71% 和 64%, 化合物 **6v** 对油菜炭疽病菌的抑制率为 72%, 均优于对照药噁霉灵(分别为 51%、61%和 70%)。此外, 部分化合物在 100  $\mu\text{g/mL}$  浓度下也表现出较好的抗植物病原细菌活性。最后, 对目标化合物的抗真菌活性与其分子结构之间的相互关系进行了初步探讨, 这为今后开发更高效的农用抗真菌剂提供有益的参考。

## 3 实验部分

### 3.1 仪器与试剂

X-4 型数字显示显微熔点测定仪(温度未校正, 北京泰克仪器); 德国布鲁克 AVANCE III HD-400M 型 400 MHz 核磁共振仪(TMS 为内标, DMSO- $d_6$  为溶剂); ESI-HRMS 数据由 Thermo Scientific Q Exactive 质谱仪测定; 晶体数据由 Bruker Smart Apex-CCD 型 X-ray 单晶衍射仪测定。所用试剂为市售分析纯或化学纯, 溶剂使用前按照常规方法进行处理。中间体 **1~4** 参照文献[9]合成。

### 3.2 实验方法

#### 3.2.1 中间体 1-(6-氟喹唑啉-4-基)哌啶-4-甲酰胺(**5a~5y**)的合成

将中间体 **4** (1.00 mmol)、20 mL 无水乙醇和 0.5 mL 冰醋酸加入到 50 mL 圆底烧瓶中, 再加入芳醛(1.20 mmol)并升温回流反应 6~8 h。停止反应, 减压浓缩反应液, 加入石油醚后抽滤, 滤饼用石油醚洗涤, 烘干得甲酰胺 **5a~5y**, 未经分离纯化直接用于下一步反应。

#### 3.2.2 中间体 **7a~7y** 的合成

于 50 mL 圆底烧瓶中加入中间体 **4** (1.00 mmol)、无水  $\text{K}_2\text{CO}_3$  (1.20 mmol)和无水二氯甲烷(25 mL), 搅拌均匀后向该体系中缓慢滴加含酰氯(1.20 mmol)的二氯甲烷溶液(5.0 mL), 室温反应 8~12 h 后停止, 静置, 抽滤, 无水乙醇重结晶得双酰肼 **7a~7y**。

1-(6-氟喹唑啉-4-基)-*N'*-(2-甲基苯甲酰基)哌啶-4-甲酰胺(**7a**): 淡黄色固体, 收率 79.4%。m.p. 201~202  $^{\circ}\text{C}$ ;

$^1\text{H}$  NMR (400 MHz, DMSO- $d_6$ )  $\delta$ : 10.02 (s, 1H), 9.97 (s, 1H), 8.64 (s, 1H), 7.90 (dd,  $J=8.0, 4.0$  Hz, 1H), 7.76 (td,  $J=8.0, 4.0$  Hz, 1H), 7.70 (dd,  $J=8.0, 4.0$  Hz, 1H), 7.37 (t,  $J=8.0$  Hz, 2H), 7.29~7.23 (m, 2H), 4.29 (d,  $J=12.0$  Hz, 2H), 3.25 (t,  $J=8.0$  Hz, 2H), 2.68~2.60 (m, 1H), 2.39 (s, 3H), 1.94~1.81 (m, 4H);  $^{13}\text{C}$  NMR (100 MHz, DMSO- $d_6$ )  $\delta$ : 173.4, 168.2, 163.7 (d,  $^4J_{\text{C-F}}=5.0$  Hz), 158.5 (d,  $^1J_{\text{C-F}}=244.0$  Hz), 153.3 (d,  $^4J_{\text{C-F}}=2.0$  Hz), 148.5, 135.9, 134.9, 131.0 (d,  $^3J_{\text{C-F}}=9.0$  Hz), 130.5, 129.9, 127.4, 125.5, 122.5 (d,  $^2J_{\text{C-F}}=25.0$  Hz), 116.6 (d,  $^3J_{\text{C-F}}=9.0$  Hz), 109.4 (d,  $^2J_{\text{C-F}}=24.0$  Hz), 48.8, 40.0, 28.2, 19.4; HRMS (ESI) calcd for  $\text{C}_{22}\text{H}_{23}\text{FN}_5\text{O}_2$   $[\text{M}+\text{H}]^+$  408.1830, found 408.1818.

1-(6-氟喹唑啉-4-基)-*N'*-(3-甲基苯甲酰基)哌啶-4-甲酰胺(**7b**): 淡黄色固体, 收率 57.9%。m.p. 148~149  $^{\circ}\text{C}$ ;  $^1\text{H}$  NMR (400 MHz, DMSO- $d_6$ )  $\delta$ : 10.32 (s, 1H), 9.98 (s, 1H), 8.65 (s, 1H), 7.90 (dd,  $J=8.0, 4.0$  Hz, 1H), 7.76 (td,  $J=8.0, 4.0$  Hz, 1H), 7.71 (s, 1H), 7.69~7.67 (m, 2H), 7.42 (d,  $J=4.0$  Hz, 1H), 7.38 (d,  $J=4.0$  Hz, 1H), 4.29 (d,  $J=16.0$  Hz, 2H), 3.25 (t,  $J=8.0$  Hz, 2H), 2.70~2.62 (m, 1H), 2.37 (s, 3H), 1.94~1.81 (m, 4H);  $^{13}\text{C}$  NMR (100 MHz, DMSO- $d_6$ )  $\delta$ : 173.5, 165.6, 163.7 (d,  $^4J_{\text{C-F}}=4.0$  Hz), 158.5 (d,  $^1J_{\text{C-F}}=244.0$  Hz), 153.3 (d,  $^4J_{\text{C-F}}=2.0$  Hz), 148.5, 137.8, 132.5, 132.4, 131.0 (d,  $^3J_{\text{C-F}}=8.0$  Hz), 128.4, 128.1, 124.6, 122.5 (d,  $^2J_{\text{C-F}}=25.0$  Hz), 116.5 (d,  $^3J_{\text{C-F}}=9.0$  Hz), 109.4 (d,  $^2J_{\text{C-F}}=23.0$  Hz), 48.8, 40.0, 28.2, 21.0; HRMS (ESI) calcd for  $\text{C}_{22}\text{H}_{23}\text{FN}_5\text{O}_2$   $[\text{M}+\text{H}]^+$  408.1830, found 408.1823.

1-(6-氟喹唑啉-4-基)-*N'*-(4-甲基苯甲酰基)哌啶-4-甲酰胺(**7c**): 淡黄色固体, 收率 67.1%。m.p. 214~215  $^{\circ}\text{C}$ ;  $^1\text{H}$  NMR (400 MHz, DMSO- $d_6$ )  $\delta$ : 10.29 (s, 1H), 9.95 (s, 1H), 8.65 (s, 1H), 7.90 (dd,  $J=8.0, 4.0$  Hz, 1H), 7.79 (d,  $J=8.0$  Hz, 2H), 7.76 (td,  $J=8.0, 4.0$  Hz, 1H), 7.70 (dd,  $J=8.0, 4.0$  Hz, 1H), 7.30 (d,  $J=8.0$  Hz, 2H), 4.29 (d,  $J=16.0$  Hz, 2H), 3.25 (t,  $J=8.0$  Hz, 2H), 2.70~2.62 (m, 1H), 2.37 (s, 3H), 1.94~1.81 (m, 4H);  $^{13}\text{C}$  NMR (100 MHz, DMSO- $d_6$ )  $\delta$ : 173.5, 165.4, 163.7 (d,  $^4J_{\text{C-F}}=4.0$  Hz), 158.5 (d,  $^1J_{\text{C-F}}=243.0$  Hz), 153.3 (d,  $^4J_{\text{C-F}}=1.0$  Hz), 148.5, 141.8, 131.0 (d,  $^3J_{\text{C-F}}=9.0$  Hz), 129.7, 129.0, 127.5, 122.5 (d,  $^2J_{\text{C-F}}=25.0$  Hz), 116.5 (d,  $^3J_{\text{C-F}}=9.0$  Hz), 109.4 (d,  $^2J_{\text{C-F}}=23.0$  Hz), 48.8, 40.0, 28.2, 21.1; HRMS (ESI) calcd for  $\text{C}_{22}\text{H}_{23}\text{FN}_5\text{O}_2$   $[\text{M}+\text{H}]^+$  408.1830, found 408.1819.

*N'*-(2-氟苯甲酰基)-1-(6-氟喹唑啉-4-基)哌啶-4-甲酰胺(**7d**): 白色固体, 收率 75.4%。m.p. 228~229  $^{\circ}\text{C}$ ;  $^1\text{H}$  NMR (400 MHz, DMSO- $d_6$ )  $\delta$ : 10.21 (s, 1H), 10.09 (s, 1H), 8.64 (s, 1H), 7.90 (dd,  $J=8.0, 4.0$  Hz, 1H), 7.75 (td,

$J=8.0, 4.0$  Hz, 1H), 7.69 (dd,  $J=8.0, 4.0$  Hz, 1H), 7.65~7.60 (m, 1H), 7.59~7.55 (m, 1H), 7.34~7.29 (m, 2H), 4.29 (d,  $J=16.0$  Hz, 2H), 3.26 (t,  $J=8.0$  Hz, 2H), 2.69~2.61 (m, 1H), 1.94~1.80 (m, 4H);  $^{13}\text{C}$  NMR (100 MHz, DMSO- $d_6$ )  $\delta$ : 173.2, 163.7 (d,  $^3J_{\text{C-F}}=4.0$  Hz), 163.2 (d,  $^4J_{\text{C-F}}=2.0$  Hz), 159.3 (d,  $^1J_{\text{C-F}}=249.0$  Hz), 158.5 (d,  $^1J_{\text{C-F}}=243.0$  Hz), 153.3 (d,  $^4J_{\text{C-F}}=1.0$  Hz), 148.3, 133.1 (d,  $^3J_{\text{C-F}}=8.0$  Hz), 130.8 (d,  $^3J_{\text{C-F}}=8.0$  Hz), 130.2 (d,  $^3J_{\text{C-F}}=4.0$  Hz), 124.6 (d,  $^4J_{\text{C-F}}=3.0$  Hz), 122.6 (d,  $^2J_{\text{C-F}}=25.0$  Hz), 122.3 (d,  $^2J_{\text{C-F}}=14.0$  Hz), 116.5 (d,  $^3J_{\text{C-F}}=8.0$  Hz), 116.3 (d,  $^2J_{\text{C-F}}=22.0$  Hz), 109.5 (d,  $^2J_{\text{C-F}}=23.0$  Hz), 48.8, 40.0, 28.2; HRMS (ESI) calcd for  $\text{C}_{21}\text{H}_{20}\text{F}_2\text{N}_5\text{O}_2$   $[\text{M}+\text{H}]^+$  412.1580, found 412.1572.

$N'$ -(3-氟苯甲酰基)-1-(6-氟喹啉-4-基)哌啶-4-甲酰肼(**7e**): 浅白色固体, 收率 70.7%. m.p. 231~232 °C;  $^1\text{H}$  NMR (400 MHz, DMSO- $d_6$ )  $\delta$ : 10.52 (s, 1H), 10.06 (s, 1H), 8.65 (s, 1H), 7.90 (dd,  $J=8.0, 4.0$  Hz, 1H), 7.76 (td,  $J=8.0, 4.0$  Hz, 1H), 7.75 (d,  $J=8.0$  Hz, 1H), 7.72~7.65 (m, 2H), 7.58 (td,  $J=8.0, 4.0$  Hz, 1H), 7.45 (td,  $J=8.0, 2.0$  Hz, 1H), 4.29 (d,  $J=16.0$  Hz, 2H), 3.25 (t,  $J=8.0$  Hz, 2H), 2.70~2.63 (m, 1H), 1.94~1.81 (m, 4H);  $^{13}\text{C}$  NMR (100 MHz, DMSO- $d_6$ )  $\delta$ : 173.5, 164.2 (d,  $^4J_{\text{C-F}}=3.0$  Hz), 163.7 (d,  $^4J_{\text{C-F}}=5.0$  Hz), 162.0 (d,  $^1J_{\text{C-F}}=243.0$  Hz), 158.5 (d,  $^1J_{\text{C-F}}=243.0$  Hz), 153.3 (d,  $^4J_{\text{C-F}}=2.0$  Hz), 148.5, 134.8 (d,  $^3J_{\text{C-F}}=7.0$  Hz), 131.0 (d,  $^3J_{\text{C-F}}=9.0$  Hz), 130.8 (d,  $^3J_{\text{C-F}}=8.0$  Hz), 123.6 (d,  $^4J_{\text{C-F}}=2.0$  Hz), 122.5 (d,  $^2J_{\text{C-F}}=24.0$  Hz), 118.8 (d,  $^2J_{\text{C-F}}=21.0$  Hz), 116.6 (d,  $^3J_{\text{C-F}}=8.0$  Hz), 114.3 (d,  $^2J_{\text{C-F}}=23.0$  Hz), 109.4 (d,  $^2J_{\text{C-F}}=23.0$  Hz), 48.8, 40.0, 28.2; HRMS (ESI) calcd for  $\text{C}_{21}\text{H}_{20}\text{F}_2\text{N}_5\text{O}_2$   $[\text{M}+\text{H}]^+$  412.1580, found 412.1570.

$N'$ -(4-氟苯甲酰基)-1-(6-氟喹啉-4-基)哌啶-4-甲酰肼(**7f**): 白色固体, 收率 80.4%. m.p. 213~214 °C;  $^1\text{H}$  NMR (400 MHz, DMSO- $d_6$ )  $\delta$ : 10.43 (s, 1H), 10.03 (s, 1H), 8.65 (s, 1H), 8.00~7.94 (m, 2H), 7.91 (dd,  $J=8.0, 4.0$  Hz, 1H), 7.77 (td,  $J=8.0, 4.0$  Hz, 1H), 7.70 (dd,  $J=8.0, 4.0$  Hz, 1H), 7.37~7.33 (m, 2H), 4.30 (d,  $J=16.0$  Hz, 2H), 3.26 (t,  $J=8.0$  Hz, 2H), 2.71~2.64 (m, 1H), 1.95~1.81 (m, 4H);  $^{13}\text{C}$  NMR (100 MHz, DMSO- $d_6$ )  $\delta$ : 173.7, 164.6, 164.3 (d,  $^1J_{\text{C-F}}=248.0$  Hz), 163.8 (d,  $^4J_{\text{C-F}}=4.0$  Hz), 158.6 (d,  $^1J_{\text{C-F}}=243.0$  Hz), 153.4 (d,  $^4J_{\text{C-F}}=1.0$  Hz), 148.5, 131.1 (d,  $^3J_{\text{C-F}}=9.0$  Hz), 130.2 (d,  $^3J_{\text{C-F}}=9.0$  Hz), 129.0 (d,  $^4J_{\text{C-F}}=3.0$  Hz), 122.6 (d,  $^2J_{\text{C-F}}=25.0$  Hz), 116.6 (d,  $^3J_{\text{C-F}}=9.0$  Hz), 115.6 (d,  $^2J_{\text{C-F}}=21.0$  Hz), 109.5 (d,  $^2J_{\text{C-F}}=23.0$  Hz), 48.8, 40.1, 28.2; HRMS (ESI) calcd for  $\text{C}_{21}\text{H}_{20}\text{F}_2\text{N}_5\text{O}_2$   $[\text{M}+\text{H}]^+$  412.1580, found 412.1570.

$N'$ -(2-氯苯甲酰基)-1-(6-氟喹啉-4-基)哌啶-4-甲酰肼(**7g**): 白色固体, 收率 85.6%. m.p. 216~217 °C;  $^1\text{H}$  NMR (400 MHz, DMSO- $d_6$ )  $\delta$ : 10.29 (s, 1H), 10.12 (s, 1H), 8.63 (s, 1H), 7.89 (dd,  $J=8.0, 4.0$  Hz, 1H), 7.75 (td,  $J=8.0, 4.0$  Hz, 1H), 7.68 (dd,  $J=8.0, 4.0$  Hz, 1H), 7.53~7.47 (m, 3H), 7.46~7.41 (m, 1H), 4.28 (d,  $J=12.0$  Hz, 2H), 3.24 (t,  $J=8.0$  Hz, 2H), 2.69~2.61 (m, 1H), 1.93~1.80 (m, 4H);  $^{13}\text{C}$  NMR (100 MHz, DMSO- $d_6$ )  $\delta$ : 173.3, 165.5, 163.8 (d,  $^4J_{\text{C-F}}=4.0$  Hz), 158.6 (d,  $^1J_{\text{C-F}}=243.0$  Hz), 153.4 (d,  $^4J_{\text{C-F}}=1.0$  Hz), 148.5, 134.7, 131.6, 131.0 (d,  $^3J_{\text{C-F}}=8.0$  Hz), 130.5, 130.0, 129.5, 127.3, 122.6 (d,  $^2J_{\text{C-F}}=25.0$  Hz), 116.6 (d,  $^3J_{\text{C-F}}=9.0$  Hz), 109.5 (d,  $^2J_{\text{C-F}}=23.0$  Hz), 48.8, 40.0, 28.2; HRMS (ESI) calcd for  $\text{C}_{21}\text{H}_{20}\text{FClN}_5\text{O}_2$   $[\text{M}+\text{H}]^+$  428.1284, found 428.1275.

$N'$ -(3-氯苯甲酰基)-1-(6-氟喹啉-4-基)哌啶-4-甲酰肼(**7h**): 白色固体, 收率 60.1%. m.p. 245~246 °C;  $^1\text{H}$  NMR (400 MHz, DMSO- $d_6$ )  $\delta$ : 10.54 (s, 1H), 10.08 (s, 1H), 8.65 (s, 1H), 7.92 (s, 1H), 7.89 (dd,  $J=8.0, 4.0$  Hz, 1H), 7.86 (d,  $J=4.0$  Hz, 1H), 7.76 (td,  $J=8.0, 4.0$  Hz, 1H), 7.71~7.66 (m, 2H), 7.56 (t,  $J=8.0$  Hz, 1H), 4.30 (d,  $J=16.0$  Hz, 2H), 3.27 (t,  $J=8.0$  Hz, 2H), 2.72~2.64 (m, 1H), 1.95~1.82 (m, 4H);  $^{13}\text{C}$  NMR (100 MHz, DMSO- $d_6$ )  $\delta$ : 173.6, 164.3, 163.8 (d,  $^4J_{\text{C-F}}=5.0$  Hz), 158.6 (d,  $^1J_{\text{C-F}}=243.0$  Hz), 153.3 (d,  $^4J_{\text{C-F}}=1.0$  Hz), 148.4, 134.5, 133.4, 131.8, 131.0 (d,  $^3J_{\text{C-F}}=9.0$  Hz), 130.7, 127.3, 126.3, 122.6 (d,  $^2J_{\text{C-F}}=25.0$  Hz), 116.6 (d,  $^3J_{\text{C-F}}=8.0$  Hz), 109.5 (d,  $^2J_{\text{C-F}}=23.0$  Hz), 48.8, 40.0, 28.2; HRMS (ESI) calcd for  $\text{C}_{21}\text{H}_{20}\text{FCIN}_5\text{O}_2$   $[\text{M}+\text{H}]^+$  428.1284, found 428.1278.

$N'$ -(4-氯苯甲酰基)-1-(6-氟喹啉-4-基)哌啶-4-甲酰肼(**7i**): 白色固体, 收率 66.9%. m.p. 249~250 °C;  $^1\text{H}$  NMR (400 MHz, DMSO- $d_6$ )  $\delta$ : 10.48 (s, 1H), 10.04 (s, 1H), 8.65 (s, 1H), 7.91 (d,  $J=8.0$  Hz, 2H), 7.90 (dd,  $J=8.0, 4.0$  Hz, 1H), 7.76 (td,  $J=8.0, 4.0$  Hz, 1H), 7.69 (dd,  $J=8.0, 4.0$  Hz, 1H), 7.59 (d,  $J=8.0$  Hz, 2H), 4.29 (d,  $J=16.0$  Hz, 2H), 3.26 (t,  $J=8.0$  Hz, 2H), 2.71~2.64 (m, 1H), 1.94~1.81 (m, 4H);  $^{13}\text{C}$  NMR (100 MHz, DMSO- $d_6$ )  $\delta$ : 173.5, 164.5, 163.7 (d,  $^4J_{\text{C-F}}=4.0$  Hz), 158.5 (d,  $^1J_{\text{C-F}}=243.0$  Hz), 153.3 (d,  $^4J_{\text{C-F}}=1.0$  Hz), 148.4, 136.7, 131.3, 131.0 (d,  $^3J_{\text{C-F}}=8.0$  Hz), 129.4, 128.6, 122.4 (d,  $^2J_{\text{C-F}}=24.0$  Hz), 116.5 (d,  $^3J_{\text{C-F}}=9.0$  Hz), 109.4 (d,  $^2J_{\text{C-F}}=23.0$  Hz), 48.7, 40.0, 28.2; HRMS (ESI) calcd for  $\text{C}_{21}\text{H}_{20}\text{FCIN}_5\text{O}_2$   $[\text{M}+\text{H}]^+$  428.1284, found 428.1277.

$N'$ -(2-溴苯甲酰基)-1-(6-氟喹啉-4-基)哌啶-4-甲酰肼(**7j**): 白色固体, 收率 70.5%. m.p. 240~241 °C;  $^1\text{H}$  NMR (400 MHz, DMSO- $d_6$ )  $\delta$ : 10.27 (s, 1H), 10.12 (s,

1H), 8.64 (s, 1H), 7.90 (dd,  $J=8.0, 4.0$  Hz, 1H), 7.76 (td,  $J=8.0, 4.0$  Hz, 1H), 7.69 (d,  $J=8.0$  Hz, 2H), 7.49~7.46 (m, 2H), 7.43~7.39 (m, 1H), 4.29 (d,  $J=16.0$  Hz, 2H), 3.25 (t,  $J=8.0$  Hz, 2H), 2.69~2.62 (m, 1H), 1.94~1.81 (m, 4H);  $^{13}\text{C}$  NMR (100 MHz, DMSO- $d_6$ )  $\delta$ : 173.2, 166.2, 163.7 (d,  $^4J_{\text{C-F}}=4.0$  Hz), 158.5 (d,  $^1J_{\text{C-F}}=243.0$  Hz), 153.3 (d,  $^4J_{\text{C-F}}=2.0$  Hz), 148.4, 136.8, 133.0, 131.6, 131.0 (d,  $^3J_{\text{C-F}}=9.0$  Hz), 129.4, 127.6, 122.4 (d,  $^2J_{\text{C-F}}=24.0$  Hz), 119.3, 116.5 (d,  $^3J_{\text{C-F}}=9.0$  Hz), 109.4 (d,  $^2J_{\text{C-F}}=23.0$  Hz), 48.7, 39.9, 28.1; HRMS (ESI) calcd for  $\text{C}_{21}\text{H}_{20}\text{FBrN}_5\text{O}_2$   $[\text{M}+\text{H}]^+$  472.0779, found 472.0770.

*N'*-(3-溴苯甲酰基)-1-(6-氟喹啉-4-基)哌啶-4-甲酰肼(**7k**): 白色固体, 收率 74.2%. m.p. 232~233 °C;  $^1\text{H}$  NMR (400 MHz, DMSO- $d_6$ )  $\delta$ : 10.51 (s, 1H), 10.06 (s, 1H), 8.64 (s, 1H), 8.06 (t,  $J=4.0$  Hz, 1H), 7.92~7.88 (m, 2H), 7.81~7.79 (m, 1H), 7.76 (td,  $J=8.0, 4.0$  Hz, 1H), 7.70 (dd,  $J=8.0, 4.0$  Hz, 1H), 7.49 (t,  $J=8.0$  Hz, 1H), 4.29 (d,  $J=16.0$  Hz, 2H), 3.25 (t,  $J=8.0$  Hz, 2H), 2.70~2.63 (m, 1H), 1.94~1.81 (m, 4H);  $^{13}\text{C}$  NMR (100 MHz, DMSO- $d_6$ )  $\delta$ : 173.4, 164.0, 163.7 (d,  $^4J_{\text{C-F}}=4.0$  Hz), 158.5 (d,  $^1J_{\text{C-F}}=243.0$  Hz), 153.3 (d,  $^4J_{\text{C-F}}=1.0$  Hz), 148.4, 134.7, 134.6, 131.0 (d,  $^3J_{\text{C-F}}=8.0$  Hz), 130.8, 130.1, 126.5, 122.5 (d,  $^2J_{\text{C-F}}=25.0$  Hz), 121.8, 116.5 (d,  $^3J_{\text{C-F}}=9.0$  Hz), 109.4 (d,  $^2J_{\text{C-F}}=23.0$  Hz), 48.7, 40.0, 28.1; HRMS (ESI) calcd for  $\text{C}_{21}\text{H}_{20}\text{FBrN}_5\text{O}_2$   $[\text{M}+\text{H}]^+$  472.0779, found 472.0771.

*N'*-(4-溴苯甲酰基)-1-(6-氟喹啉-4-基)哌啶-4-甲酰肼(**7l**): 淡黄色固体, 收率 81.0%. m.p. > 250 °C;  $^1\text{H}$  NMR (400 MHz, DMSO- $d_6$ )  $\delta$ : 10.47 (s, 1H), 10.01 (s, 1H), 8.64 (s, 1H), 7.90 (dd,  $J=8.0, 4.0$  Hz, 1H), 7.82 (d,  $J=8.0$  Hz, 2H), 7.79~7.74 (m, 1H), 7.73 (d,  $J=8.0$  Hz, 2H), 7.70 (dd,  $J=8.0, 4.0$  Hz, 1H), 4.29 (d,  $J=12.0$  Hz, 2H), 3.25 (t,  $J=8.0$  Hz, 2H), 2.70~2.62 (m, 1H), 1.94~1.81 (m, 4H);  $^{13}\text{C}$  NMR (100 MHz, DMSO- $d_6$ )  $\delta$ : 173.5, 164.6, 163.7 (d,  $^4J_{\text{C-F}}=4.0$  Hz), 158.5 (d,  $^1J_{\text{C-F}}=244.0$  Hz), 153.3 (d,  $^4J_{\text{C-F}}=1.0$  Hz), 148.4, 131.7, 131.6, 131.0 (d,  $^3J_{\text{C-F}}=8.0$  Hz), 129.5, 125.6, 122.5 (d,  $^2J_{\text{C-F}}=25.0$  Hz), 116.5 (d,  $^3J_{\text{C-F}}=8.0$  Hz), 109.4 (d,  $^2J_{\text{C-F}}=23.0$  Hz), 48.7, 40.0, 28.1; HRMS (ESI) calcd for  $\text{C}_{21}\text{H}_{20}\text{FBrN}_5\text{O}_2$   $[\text{M}+\text{H}]^+$  472.0779, found 472.0770.

1-(6-氟喹啉-4-基)-*N'*-(2-硝基苯甲酰基)哌啶-4-甲酰肼(**7m**): 黄色固体, 收率 74.9%. m.p. > 250 °C;  $^1\text{H}$  NMR (400 MHz, DMSO- $d_6$ )  $\delta$ : 10.58 (s, 1H), 10.26 (s, 1H), 8.65 (s, 1H), 8.16 (d,  $J=8.0$  Hz, 1H), 8.09 (d,  $J=8.0$  Hz, 1H), 7.90 (dd,  $J=8.0, 4.0$  Hz, 1H), 7.87~7.84 (m,

1H), 7.78~7.74 (m, 1H), 7.71~7.70 (m, 1H), 7.69~7.67 (m, 1H), 4.29 (d,  $J=16.0$  Hz, 2H), 3.24 (t,  $J=8.0$  Hz, 2H), 2.71~2.64 (m, 1H), 1.93~1.81 (m, 4H);  $^{13}\text{C}$  NMR (100 MHz, DMSO- $d_6$ )  $\delta$ : 173.2, 164.4, 163.7 (d,  $^4J_{\text{C-F}}=4.0$  Hz), 158.5 (d,  $^1J_{\text{C-F}}=244.0$  Hz), 153.3 (d,  $^4J_{\text{C-F}}=2.0$  Hz), 148.5, 147.6, 133.8, 133.7, 131.0 (d,  $^3J_{\text{C-F}}=9.0$  Hz), 130.6, 124.4, 123.2, 122.5 (d,  $^3J_{\text{C-F}}=24.0$  Hz), 116.5 (d,  $^3J_{\text{C-F}}=8.0$  Hz), 109.4 (d,  $^2J_{\text{C-F}}=23.0$  Hz), 48.7, 40.0, 28.1; HRMS (ESI) calcd for  $\text{C}_{21}\text{H}_{20}\text{FN}_6\text{O}_4$   $[\text{M}+\text{H}]^+$  439.1525, found 439.1516.

1-(6-氟喹啉-4-基)-*N'*-(3-硝基苯甲酰基)哌啶-4-甲酰肼(**7n**): 淡白色固体, 收率 63.7%. m.p. 245~246 °C;  $^1\text{H}$  NMR (400 MHz, DMSO- $d_6$ )  $\delta$ : 10.82 (s, 1H), 10.16 (s, 1H), 8.72 (s, 1H), 8.65 (s, 1H), 8.44 (d,  $J=8.0$  Hz, 1H), 8.32 (d,  $J=8.0$  Hz, 1H), 7.90 (dd,  $J=8.0, 4.0$  Hz, 1H), 7.83 (t,  $J=8.0$  Hz, 1H), 7.76 (td,  $J=8.0, 4.0$  Hz, 1H), 7.70 (dd,  $J=8.0, 4.0$  Hz, 1H), 4.30 (d,  $J=12.0$  Hz, 2H), 3.26 (t,  $J=8.0$  Hz, 2H), 2.73~2.65 (m, 1H), 1.95~1.80 (m, 4H);  $^{13}\text{C}$  NMR (100 MHz, DMSO- $d_6$ )  $\delta$ : 173.4, 163.7 (d,  $^4J_{\text{C-F}}=4.0$  Hz), 163.5, 158.5 (d,  $^1J_{\text{C-F}}=243.0$  Hz), 153.3 (d,  $^4J_{\text{C-F}}=1.0$  Hz), 148.5, 147.9, 133.9, 133.8, 131.0 (d,  $^3J_{\text{C-F}}=9.0$  Hz), 130.5, 126.5, 122.5 (d,  $^2J_{\text{C-F}}=24.0$  Hz), 122.2, 116.6 (d,  $^3J_{\text{C-F}}=9.0$  Hz), 109.4 (d,  $^2J_{\text{C-F}}=23.0$  Hz), 48.7, 40.0, 28.2; HRMS (ESI) calcd for  $\text{C}_{21}\text{H}_{20}\text{FN}_6\text{O}_4$   $[\text{M}+\text{H}]^+$  439.1525, found 439.1516.

1-(6-氟喹啉-4-基)-*N'*-(4-硝基苯甲酰基)哌啶-4-甲酰肼(**7o**): 淡黄色固体, 收率 71.1%. m.p. 241~242 °C;  $^1\text{H}$  NMR (400 MHz, DMSO- $d_6$ )  $\delta$ : 10.78 (s, 1H), 10.16 (s, 1H), 8.64 (s, 1H), 8.34 (d,  $J=8.0$  Hz, 2H), 8.11 (d,  $J=8.0$  Hz, 2H), 7.89 (s, 1H), 7.76~7.64 (m, 2H), 4.30 (d,  $J=8.0$  Hz, 2H), 3.28~3.23 (m, 2H), 2.73~2.62 (m, 1H), 1.98~1.81 (m, 4H);  $^{13}\text{C}$  NMR (100 MHz, DMSO- $d_6$ )  $\delta$ : 173.4, 164.0, 163.7 (d,  $^4J_{\text{C-F}}=3.0$  Hz), 158.5 (d,  $^1J_{\text{C-F}}=243.0$  Hz), 153.3 (d,  $^4J_{\text{C-F}}=1.0$  Hz), 149.4, 148.4, 138.1, 130.9 (d,  $^3J_{\text{C-F}}=9.0$  Hz), 129.0, 123.8, 122.4 (d,  $^2J_{\text{C-F}}=24.0$  Hz), 116.5 (d,  $^3J_{\text{C-F}}=8.0$  Hz), 109.4 (d,  $^2J_{\text{C-F}}=23.0$  Hz), 48.7, 40.0, 28.2; HRMS (ESI) calcd for  $\text{C}_{21}\text{H}_{20}\text{FN}_6\text{O}_4$   $[\text{M}+\text{H}]^+$  439.1525, found 439.1516.

1-(6-氟喹啉-4-基)-*N'*-(4-三氟甲基苯甲酰基)哌啶-4-甲酰肼(**7p**): 淡黄色固体, 收率 58.4%. m.p. 237~238 °C;  $^1\text{H}$  NMR (400 MHz, DMSO- $d_6$ )  $\delta$ : 10.64 (s, 1H), 10.10 (s, 1H), 8.65 (s, 1H), 8.08 (d,  $J=8.0$  Hz, 2H), 7.92~7.89 (m, 3H), 7.77 (td,  $J=8.0, 4.0$  Hz, 1H), 7.70 (dd,  $J=8.0, 4.0$  Hz, 1H), 4.30 (d,  $J=12.0$  Hz, 2H), 3.26 (t,  $J=8.0$  Hz, 2H), 2.72~2.64 (m, 1H), 1.95~1.82 (m, 4H);  $^{13}\text{C}$

NMR (100 MHz, DMSO- $d_6$ )  $\delta$ : 173.5, 164.4, 163.7 (d,  $^4J_{C-F}$ =4.0 Hz), 158.5 (d,  $^1J_{C-F}$ =244.0 Hz), 153.3 (d,  $^4J_{C-F}$ =2.0 Hz), 148.4, 136.3, 131.7 (q,  $^2J_{C-F}$ =32.0 Hz), 131.0 (d,  $^3J_{C-F}$ =9.0 Hz), 128.4, 125.6 (q,  $^3J_{C-F}$ =4.0 Hz), 123.9 (q,  $^1J_{C-F}$ =271.0 Hz), 122.5 (d,  $^2J_{C-F}$ =24.0 Hz), 116.6 (d,  $^3J_{C-F}$ =9.0 Hz), 109.4 (d,  $^2J_{C-F}$ =23.0 Hz), 48.7, 40.0, 28.2; HRMS (ESI) calcd for  $C_{22}H_{20}F_4N_5O_2$  [M+H] $^+$  462.1548, found 462.1534.

*N'*-(4-氧基苯甲酰基)-1-(6-氟喹啉-4-基)哌啶-4-甲酰肼(**7q**): 黄色固体, 收率 80.3%. m.p. 240~242 °C;  $^1H$  NMR (400 MHz, DMSO- $d_6$ )  $\delta$ : 10.74 (s, 1H), 10.10 (s, 1H), 8.64 (s, 1H), 8.05 (d,  $J$ =8.0 Hz, 2H), 8.02 (d,  $J$ =4.0 Hz, 2H), 7.90 (dd,  $J$ =8.0, 4.0 Hz, 1H), 7.76 (td,  $J$ =8.0, 4.0 Hz, 1H), 7.70 (dd,  $J$ =8.0, 4.0 Hz, 1H), 4.29 (d,  $J$ =16.0 Hz, 2H), 3.26 (t,  $J$ =8.0 Hz, 2H), 2.71~2.64 (m, 1H), 1.94~1.81 (m, 4H);  $^{13}C$  NMR (100 MHz, DMSO- $d_6$ )  $\delta$ : 173.4, 164.2, 163.7 (d,  $^4J_{C-F}$ =4.0 Hz), 158.5 (d,  $^1J_{C-F}$ =244.0 Hz), 153.3 (d,  $^4J_{C-F}$ =2.0 Hz), 148.4, 136.5, 132.6, 131.0 (d,  $^3J_{C-F}$ =9.0 Hz), 128.3, 122.5 (d,  $^2J_{C-F}$ =25.0 Hz), 118.2, 116.5 (d,  $^3J_{C-F}$ =9.0 Hz), 114.2, 109.4 (d,  $^2J_{C-F}$ =23.0 Hz), 48.7, 40.0, 28.1; HRMS (ESI) calcd for  $C_{22}H_{20}FN_6O_2$  [M+H] $^+$  419.1626, found 419.1614.

1-(6-氟喹啉-4-基)-*N'*-(4-甲氧基苯甲酰基)哌啶-4-甲酰肼(**7r**): 灰色固体, 收率 64.5%. m.p. 218~219 °C;  $^1H$  NMR (400 MHz, DMSO- $d_6$ )  $\delta$ : 10.22 (s, 1H), 9.92 (s, 1H), 8.64 (s, 1H), 7.92~7.86 (m, 3H), 7.76 (td,  $J$ =8.0, 4.0 Hz, 1H), 7.70 (dd,  $J$ =8.0, 4.0 Hz, 1H), 7.03 (d,  $J$ =8.0 Hz, 2H), 4.29 (d,  $J$ =12.0 Hz, 2H), 3.82 (s, 3H), 3.25 (t,  $J$ =8.0 Hz, 2H), 2.68~2.62 (m, 1H), 1.92~1.81 (m, 4H);  $^{13}C$  NMR (100 MHz, DMSO- $d_6$ )  $\delta$ : 173.6, 165.1, 163.8 (d,  $^4J_{C-F}$ =5.0 Hz), 162.0, 158.5 (d,  $^1J_{C-F}$ =243.0 Hz), 153.4 (d,  $^4J_{C-F}$ =1.0 Hz), 148.5, 131.0 (d,  $^3J_{C-F}$ =8.0 Hz), 129.4, 124.7, 122.5 (d,  $^2J_{C-F}$ =24.0 Hz), 116.6 (d,  $^3J_{C-F}$ =8.0 Hz), 113.7, 109.4 (d,  $^2J_{C-F}$ =23.0 Hz), 55.5, 48.8, 40.0, 28.2; HRMS (ESI) calcd for  $C_{22}H_{23}FN_5O_3$  [M+H] $^+$  424.1779, found 424.1769.

1-(6-氟喹啉-4-基)-*N'*-(4-三氟甲氧基苯甲酰基)哌啶-4-甲酰肼(**7s**): 白色固体, 收率 83.8%. m.p. 238~239 °C;  $^1H$  NMR (400 MHz, DMSO- $d_6$ )  $\delta$ : 10.49 (s, 1H), 10.07 (s, 1H), 8.65 (s, 1H), 8.01 (d,  $J$ =8.0 Hz, 2H), 7.90 (dd,  $J$ =8.0, 4.0 Hz, 1H), 7.76 (td,  $J$ =8.0, 4.0 Hz, 1H), 7.70 (dd,  $J$ =8.0, 4.0 Hz, 1H), 7.51 (d,  $J$ =8.0 Hz, 2H), 4.29 (d,  $J$ =12.0 Hz, 2H), 3.26 (t,  $J$ =8.0 Hz, 2H), 2.70~2.64 (m, 1H), 1.94~1.81 (m, 4H);  $^{13}C$  NMR (100 MHz, DMSO- $d_6$ )  $\delta$ : 173.4, 164.3, 163.7 (d,  $^4J_{C-F}$ =4.0 Hz), 158.5

(d,  $^1J_{C-F}$ =244.0 Hz), 153.3 (d,  $^4J_{C-F}$ =1.0 Hz), 150.7, 148.5, 131.7, 131.0 (d,  $^3J_{C-F}$ =9.0 Hz), 129.8, 122.5 (d,  $^2J_{C-F}$ =25.0 Hz), 120.9, 120.0 (q,  $^1J_{C-F}$ =256.0 Hz), 116.6 (d,  $^3J_{C-F}$ =9.0 Hz), 109.4 (d,  $^2J_{C-F}$ =23.0 Hz), 48.8, 40.0, 28.2; HRMS (ESI) calcd for  $C_{22}H_{20}F_4N_5O_3$  [M+H] $^+$  478.1497, found 478.1484.

*N'*-(1-(6-氟喹啉-4-基)哌啶-4-羰基)吡啶甲酰肼(**7t**): 黄色固体, 收率 80.2%. m.p. 98~99 °C;  $^1H$  NMR (400 MHz, DMSO- $d_6$ )  $\delta$ : 10.47 (s, 1H), 10.09 (s, 1H), 8.68 (d,  $J$ =4.0 Hz, 1H), 8.65 (s, 1H), 8.04 (d,  $J$ =2.0 Hz, 1H), 8.03 (t,  $J$ =2.0 Hz, 1H), 7.90 (dd,  $J$ =8.0, 4.0 Hz, 1H), 7.76 (dd,  $J$ =8.0, 4.0 Hz, 1H), 7.70 (dd,  $J$ =8.0, 4.0 Hz, 1H), 7.67~7.64 (m, 1H), 4.29 (d,  $J$ =12.0 Hz, 2H), 3.26 (t,  $J$ =8.0 Hz, 2H), 2.71~2.63 (m, 1H), 1.94~1.81 (m, 4H);  $^{13}C$  NMR (100 MHz, DMSO- $d_6$ )  $\delta$ : 173.0, 163.7 (d,  $^4J_{C-F}$ =5.0 Hz), 162.8, 158.5 (d,  $^1J_{C-F}$ =243.0 Hz), 153.2 (d,  $^4J_{C-F}$ =2.0 Hz), 149.2, 148.7, 148.3, 137.9, 130.9 (d,  $^3J_{C-F}$ =9.0 Hz), 127.0, 122.5 (d,  $^2J_{C-F}$ =25.0 Hz), 122.3, 116.5 (d,  $^3J_{C-F}$ =8.0 Hz), 109.4 (d,  $^2J_{C-F}$ =23.0 Hz), 48.7, 39.9, 28.2; HRMS (ESI) calcd for  $C_{20}H_{20}FN_6O_2$  [M+H] $^+$  395.1626, found 395.1620.

1-(6-氟喹啉-4-基)-*N'*-(噻吩-2-羰基)哌啶-4-甲酰肼(**7u**): 淡黄色固体, 收率 68.5%. m.p. 177~178 °C;  $^1H$  NMR (400 MHz, DMSO- $d_6$ )  $\delta$ : 10.41 (s, 1H), 10.01 (s, 1H), 8.63 (s, 1H), 7.89 (dd,  $J$ =8.0, 4.0 Hz, 1H), 7.85 (d,  $J$ =4.0 Hz, 1H), 7.84 (d,  $J$ =4.0 Hz, 1H), 7.75 (td,  $J$ =8.0, 4.0 Hz, 1H), 7.67 (dd,  $J$ =8.0, 4.0 Hz, 1H), 7.19 (t,  $J$ =4.0 Hz, 1H), 4.28 (d,  $J$ =16.0 Hz, 2H), 3.25 (t,  $J$ =8.0 Hz, 2H), 2.70~2.62 (m, 1H), 1.92~1.81 (m, 4H);  $^{13}C$  NMR (100 MHz, DMSO- $d_6$ )  $\delta$ : 173.7, 163.7 (d,  $^4J_{C-F}$ =4.0 Hz), 162.4, 158.5 (d,  $^1J_{C-F}$ =244.0 Hz), 153.3 (d,  $^4J_{C-F}$ =2.0 Hz), 148.4, 137.4, 131.6, 131.0 (d,  $^3J_{C-F}$ =9.0 Hz), 128.9, 128.2, 122.5 (d,  $^2J_{C-F}$ =25.0 Hz), 116.5 (d,  $^3J_{C-F}$ =9.0 Hz), 109.4 (d,  $^2J_{C-F}$ =23.0 Hz), 48.8, 40.0, 28.2; HRMS (ESI) calcd for  $C_{19}H_{19}FN_5O_2S$  [M+H] $^+$  400.1238, found 400.1228.

1-(6-氟喹啉-4-基)-*N'*-(呋喃-2-羰基)哌啶-4-甲酰肼(**7v**): 淡黄色固体, 收率 55.0%. m.p. 200~201 °C;  $^1H$  NMR (400 MHz, DMSO- $d_6$ )  $\delta$ : 10.29 (s, 1H), 9.95 (s, 1H), 8.65 (s, 1H), 7.93~7.88 (m, 2H), 7.76 (td,  $J$ =8.0, 4.0 Hz, 1H), 7.69 (dd,  $J$ =8.0, 4.0 Hz, 1H), 7.24 (d,  $J$ =4.0 Hz, 1H), 6.67 (t,  $J$ =8.0 Hz, 1H), 4.29 (d,  $J$ =12.0 Hz, 2H), 3.25 (t,  $J$ =8.0 Hz, 2H), 2.69~2.61 (m, 1H), 1.93~1.81 (m, 4H);  $^{13}C$  NMR (100 MHz, DMSO- $d_6$ )  $\delta$ : 173.6, 163.8 (d,  $^4J_{C-F}$ =5.0 Hz), 158.5 (d,  $^1J_{C-F}$ =243.0 Hz), 157.1, 153.3 (d,  $^4J_{C-F}$ =1.0 Hz), 148.4, 146.2, 145.8, 131.0 (d,  $^3J_{C-F}$ =9.0

Hz), 122.5 (d,  $^2J_{\text{C-F}}=25.0$  Hz), 116.5 (d,  $^3J_{\text{C-F}}=9.0$  Hz), 114.5, 111.9, 109.4 (d,  $^2J_{\text{C-F}}=23.0$  Hz), 48.7, 40.0, 28.2; HRMS (ESI) calcd for  $\text{C}_{19}\text{H}_{19}\text{FN}_5\text{O}_3$   $[\text{M}+\text{H}]^+$  384.1466, found 384.1456.

*N'*-(4-(叔丁基)苯甲酰基)-1-(6-氟喹啉-4-基)哌啶-4-甲酰肼(**7w**): 浅灰色固体, 收率 69.5%. m.p. 137~139 °C;  $^1\text{H}$  NMR (400 MHz,  $\text{DMSO}-d_6$ )  $\delta$ : 10.29 (s, 1H), 9.95 (s, 1H), 8.64 (s, 1H), 7.90 (dd,  $J=8.0, 4.0$  Hz, 1H), 7.83 (d,  $J=8.0$  Hz, 2H), 7.76 (td,  $J=8.0, 4.0$  Hz, 1H), 7.70 (dd,  $J=8.0, 4.0$  Hz, 1H), 7.51 (d,  $J=8.0$  Hz, 2H), 4.29 (d,  $J=12.0$  Hz, 2H), 3.26 (t,  $J=8.0$  Hz, 2H), 2.70~2.62 (m, 1H), 1.94~1.81 (m, 4H), 1.30 (s, 9H);  $^{13}\text{C}$  NMR (100 MHz,  $\text{DMSO}-d_6$ )  $\delta$ : 173.5, 165.4, 163.7 (d,  $^4J_{\text{C-F}}=4.0$  Hz), 158.5 (d,  $^1J_{\text{C-F}}=243.0$  Hz), 154.7, 153.3 (d,  $^4J_{\text{C-F}}=2.0$  Hz), 148.5, 131.0 (d,  $^3J_{\text{C-F}}=9.0$  Hz), 129.8, 127.3, 125.3, 122.5 (d,  $^2J_{\text{C-F}}=25.0$  Hz), 116.6 (d,  $^3J_{\text{C-F}}=8.0$  Hz), 109.4 (d,  $^2J_{\text{C-F}}=23.0$  Hz), 48.7, 40.0, 34.7, 30.9, 28.2; HRMS (ESI) calcd for  $\text{C}_{25}\text{H}_{29}\text{FN}_5\text{O}_2$   $[\text{M}+\text{H}]^+$  450.2300, found 450.2288.

*N'*-苯甲酰基-1-(6-氟喹啉-4-基)哌啶-4-甲酰肼(**7x**): 淡黄色固体, 收率 75.1%. m.p. 186~187 °C;  $^1\text{H}$  NMR (400 MHz,  $\text{DMSO}-d_6$ )  $\delta$ : 10.38 (s, 1H), 9.99 (s, 1H), 8.65 (s, 1H), 7.92~7.88 (m, 3H), 7.76 (td,  $J=8.0, 4.0$  Hz, 1H), 7.70 (dd,  $J=8.0, 4.0$  Hz, 1H), 7.58 (t,  $J=4.0$  Hz, 1H), 7.50 (t,  $J=8.0$  Hz, 2H), 4.29 (d,  $J=12.0$  Hz, 2H), 3.26 (t,  $J=8.0$  Hz, 2H), 2.71~2.63 (m, 1H), 1.94~1.82 (m, 4H);  $^{13}\text{C}$  NMR (100 MHz,  $\text{DMSO}-d_6$ )  $\delta$ : 173.5, 165.5, 163.7 (d,  $^4J_{\text{C-F}}=4.0$  Hz), 158.5 (d,  $^1J_{\text{C-F}}=243.0$  Hz), 153.3 (d,  $^4J_{\text{C-F}}=1.0$  Hz), 148.5, 132.5, 131.8, 131.0 (d,  $^3J_{\text{C-F}}=9.0$  Hz), 128.5, 127.4, 122.5 (d,  $^2J_{\text{C-F}}=25.0$  Hz), 116.5 (d,  $^3J_{\text{C-F}}=9.0$  Hz), 109.4 (d,  $^2J_{\text{C-F}}=23.0$  Hz), 48.8, 40.0, 28.2; HRMS (ESI) calcd for  $\text{C}_{21}\text{H}_{21}\text{FN}_5\text{O}_2$   $[\text{M}+\text{H}]^+$  394.1674, found 394.1665.

1-(6-氟喹啉-4-基)-*N'*-(3,4,5-三甲氧基苯甲酰基)哌啶-4-甲酰肼(**7y**): 淡黄色固体, 收率 67.3%. m.p. 135~137 °C;  $^1\text{H}$  NMR (400 MHz,  $\text{DMSO}-d_6$ )  $\delta$ : 10.33 (s, 1H), 10.00 (s, 1H), 8.64 (s, 1H), 7.90 (dd,  $J=8.0, 4.0$  Hz, 1H), 7.75 (td,  $J=8.0, 4.0$  Hz, 1H), 7.69 (dd,  $J=8.0, 4.0$  Hz, 1H), 7.28 (s, 1H), 7.24 (s, 1H), 4.29 (d,  $J=12.0$  Hz, 2H), 3.84 (s, 6H), 3.72 (s, 3H), 3.26 (t,  $J=12.0$  Hz, 2H), 2.72~2.64 (m, 1H), 1.97~1.82 (m, 4H);  $^{13}\text{C}$  NMR (100 MHz,  $\text{DMSO}-d_6$ )  $\delta$ : 173.6, 164.9, 163.7 (d,  $^4J_{\text{C-F}}=5.0$  Hz), 158.5 (d,  $^1J_{\text{C-F}}=243.0$  Hz), 153.3 (d,  $^4J_{\text{C-F}}=2.0$  Hz), 152.7, 148.5, 140.3, 131.0 (d,  $^3J_{\text{C-F}}=8.0$  Hz), 127.5, 122.5 (d,  $^2J_{\text{C-F}}=24.0$  Hz), 116.5 (d,  $^3J_{\text{C-F}}=8.0$  Hz), 109.4 (d,  $^2J_{\text{C-F}}=$

23.0 Hz), 104.9, 60.1, 56.0, 48.8, 40.0, 28.2; HRMS (ESI) calcd for  $\text{C}_{24}\text{H}_{27}\text{FN}_5\text{O}_5$   $[\text{M}+\text{H}]^+$  484.1991, found 484.1983.

### 3.2.3 目标化合物 **6a**~**6y** 的合成

在 25 mL 圆底烧瓶中加入 1.28 mmol 中间体 **5**、528 mg (3.83 mmol) 无水  $\text{K}_2\text{CO}_3$ 、422 mg (1.66 mmol)  $\text{I}_2$  以及二甲亚砜(15 mL), 搅拌升温至 100 °C 反应. TLC 监测反应, 待原料点消失后停止反应, 冷却反应液至室温, 加入 5%  $\text{Na}_2\text{S}_2\text{O}_3$  水溶液, 乙酸乙酯萃取三次, 合并有机层并用无水  $\text{Na}_2\text{SO}_4$  干燥, 浓缩后通过硅胶柱层析分离得化合物 **6a**~**6y**.

2-(1-(6-氟喹啉-4-基)哌啶-4-基)-5-(2-甲基)-1,3,4-噁二唑(**6a**): 白色固体, 收率 75.3%. m.p. 151~152 °C;  $^1\text{H}$  NMR (400 MHz,  $\text{DMSO}-d_6$ )  $\delta$ : 8.66 (s, 1H), 7.92~7.89 (m, 2H), 7.79~7.71 (m, 2H), 7.50 (t,  $J=8.0$  Hz, 1H), 7.45~7.38 (m, 2H), 4.25 (d,  $J=12.0$  Hz, 2H), 3.52~3.39 (m, 3H), 2.62 (s, 3H), 2.28~2.23 (m, 2H), 2.11~2.01 (m, 2H);  $^{13}\text{C}$  NMR (100 MHz,  $\text{DMSO}-d_6$ )  $\delta$ : 168.1, 164.1, 163.8 (d,  $^4J_{\text{C-F}}=4.0$  Hz), 158.6 (d,  $^1J_{\text{C-F}}=244.0$  Hz), 153.3 (d,  $^4J_{\text{C-F}}=2.0$  Hz), 148.4, 137.5, 131.7, 131.4, 131.0 (d,  $^3J_{\text{C-F}}=9.0$  Hz), 128.8, 126.5, 122.7, 122.5 (d,  $^2J_{\text{C-F}}=25.0$  Hz), 116.6 (d,  $^3J_{\text{C-F}}=8.0$  Hz), 109.4 (d,  $^2J_{\text{C-F}}=23.0$  Hz), 48.5, 32.4, 28.6, 21.5; HRMS (ESI) calcd for  $\text{C}_{22}\text{H}_{21}\text{FN}_5\text{O}$   $[\text{M}+\text{H}]^+$  390.1725, found 390.1713.

2-(1-(6-氟喹啉-4-基)哌啶-4-基)-5-(3-甲基)-1,3,4-噁二唑(**6b**): 淡黄色固体, 收率 60.5%. m.p. 161~162 °C;  $^1\text{H}$  NMR (400 MHz,  $\text{DMSO}-d_6$ )  $\delta$ : 8.67 (s, 1H), 7.92 (dd,  $J=8.0, 4.0$  Hz, 1H), 7.84~7.79 (m, 2H), 7.75 (td,  $J=8.0, 4.0$  Hz, 2H), 7.49 (t,  $J=8.0$  Hz, 1H), 7.44 (d,  $J=8.0$  Hz, 1H), 4.26 (d,  $J=12.0$  Hz, 2H), 3.51~3.39 (m, 3H), 2.41 (s, 3H), 2.28~2.23 (m, 2H), 2.11~2.01 (m, 2H);  $^{13}\text{C}$  NMR (100 MHz,  $\text{DMSO}-d_6$ )  $\delta$ : 168.5, 164.0, 163.8 (d,  $^4J_{\text{C-F}}=4.0$  Hz), 158.6 (d,  $^1J_{\text{C-F}}=244.0$  Hz), 153.3 (d,  $^4J_{\text{C-F}}=1.0$  Hz), 148.4, 138.9, 132.6, 131.0 (d,  $^3J_{\text{C-F}}=9.0$  Hz), 129.3, 126.8, 123.7, 123.5, 122.5 (d,  $^2J_{\text{C-F}}=25.0$  Hz), 116.6 (d,  $^3J_{\text{C-F}}=8.0$  Hz), 109.4 (d,  $^2J_{\text{C-F}}=24.0$  Hz), 48.4, 32.5, 28.6, 20.9; HRMS (ESI) calcd for  $\text{C}_{22}\text{H}_{21}\text{FN}_5\text{O}$   $[\text{M}+\text{H}]^+$  390.1725, found 390.1713.

2-(1-(6-氟喹啉-4-基)哌啶-4-基)-5-(4-甲基)-1,3,4-噁二唑(**6c**): 白色固体, 收率 58.7%. m.p. 181~182 °C;  $^1\text{H}$  NMR (400 MHz,  $\text{DMSO}-d_6$ )  $\delta$ : 8.67 (s, 1H), 7.93~7.89 (m, 3H), 7.80~7.72 (m, 2H), 7.41 (d,  $J=8.0$  Hz, 2H), 4.26 (d,  $J=16.0$  Hz, 2H), 3.51~3.39 (m, 3H), 2.40 (s, 3H), 2.27~2.23 (m, 2H), 2.10~2.01 (m, 2H);  $^{13}\text{C}$  NMR (100 MHz,  $\text{DMSO}-d_6$ )  $\delta$ : 168.3, 164.0, 163.8 (d,

$^4J_{\text{C-F}}=4.0$  Hz), 158.6 (d,  $^1J_{\text{C-F}}=244.0$  Hz), 153.3 (d,  $^4J_{\text{C-F}}=2.0$  Hz), 148.5, 142.0, 131.1 (d,  $^3J_{\text{C-F}}=9.0$  Hz), 130.0, 126.5, 122.5 (d,  $^2J_{\text{C-F}}=25.0$  Hz), 120.8, 116.6 (d,  $^3J_{\text{C-F}}=8.0$  Hz), 109.4 (d,  $^2J_{\text{C-F}}=23.0$  Hz), 48.4, 32.5, 28.7, 21.2; HRMS (ESI) calcd for  $\text{C}_{22}\text{H}_{21}\text{FN}_5\text{O}$   $[\text{M} + \text{H}]^+$  390.1725, found 390.1718.

2-(2-氟苯基)-5-(1-(6-氟喹啉-4-基)哌啶-4-基)-1,3,4-噁二唑(**6d**): 浅棕色固体, 收率 69.2%. m.p. 143~144 °C;  $^1\text{H}$  NMR (400 MHz,  $\text{DMSO}-d_6$ )  $\delta$ : 8.67 (s, 1H), 8.05 (td,  $J=8.0, 4.0$  Hz, 1H), 7.92 (dd,  $J=8.0, 4.0$  Hz, 1H), 7.80~7.67 (m, 3H), 7.50 (td,  $J=8.0, 4.0$  Hz, 1H), 7.44 (td,  $J=8.0, 4.0$  Hz, 1H), 4.26 (d,  $J=12.0$  Hz, 2H), 3.55~3.49 (m, 1H), 3.48~3.41 (m, 2H), 2.28~2.24 (m, 2H), 2.11~2.01 (m, 2H);  $^{13}\text{C}$  NMR (100 MHz,  $\text{DMSO}-d_6$ )  $\delta$ : 168.8, 163.8 (d,  $^4J_{\text{C-F}}=4.0$  Hz), 160.5 (d,  $^3J_{\text{C-F}}=11.0$  Hz), 159.2 (d,  $^1J_{\text{C-F}}=251.0$  Hz), 158.6 (d,  $^1J_{\text{C-F}}=244.0$  Hz), 153.3 (d,  $^4J_{\text{C-F}}=2.0$  Hz), 148.4, 134.1 (d,  $^3J_{\text{C-F}}=9.0$  Hz), 131.0 (d,  $^3J_{\text{C-F}}=9.0$  Hz), 129.6, 125.3 (d,  $^4J_{\text{C-F}}=4.0$  Hz), 122.5 (d,  $^2J_{\text{C-F}}=24.0$  Hz), 117.1 (d,  $^2J_{\text{C-F}}=20.0$  Hz), 116.6 (d,  $^3J_{\text{C-F}}=8.0$  Hz), 111.8 (d,  $^3J_{\text{C-F}}=12.0$  Hz), 109.4 (d,  $^2J_{\text{C-F}}=23.0$  Hz), 48.4, 32.4, 28.6; HRMS (ESI) calcd for  $\text{C}_{21}\text{H}_{18}\text{F}_2\text{N}_5\text{O}$   $[\text{M} + \text{H}]^+$  394.1474, found 394.1471.

2-(3-氟苯基)-5-(1-(6-氟喹啉-4-基)哌啶-4-基)-1,3,4-噁二唑(**6e**): 白色固体, 收率 76.1%. m.p. 192~193 °C;  $^1\text{H}$  NMR (400 MHz,  $\text{DMSO}-d_6$ )  $\delta$ : 8.67 (s, 1H), 8.10~8.06 (m, 2H), 7.92 (dd,  $J=8.0, 4.0$  Hz, 1H), 7.80~7.72 (m, 2H), 7.46 (t,  $J=8.0$  Hz, 2H), 4.26 (d,  $J=16.0$  Hz, 2H), 3.52~3.40 (m, 3H), 2.27~2.23 (m, 2H), 2.11~2.01 (m, 2H);  $^{13}\text{C}$  NMR (100 MHz,  $\text{DMSO}-d_6$ )  $\delta$ : 168.6, 164.1 (d,  $^1J_{\text{C-F}}=248.0$  Hz), 163.8 (d,  $^4J_{\text{C-F}}=4.0$  Hz), 163.2, 162.8, 158.6 (d,  $^1J_{\text{C-F}}=244.0$  Hz), 153.3 (d,  $^4J_{\text{C-F}}=2.0$  Hz), 148.5, 131.0 (d,  $^3J_{\text{C-F}}=9.0$  Hz), 129.2 (d,  $^3J_{\text{C-F}}=9.0$  Hz), 122.6 (d,  $^2J_{\text{C-F}}=25.0$  Hz), 120.3 (d,  $^4J_{\text{C-F}}=3.0$  Hz), 116.7 (d,  $^2J_{\text{C-F}}=22.0$  Hz), 116.6 (d,  $^3J_{\text{C-F}}=8.0$  Hz), 109.4 (d,  $^2J_{\text{C-F}}=23.0$  Hz), 48.4, 32.4, 28.6; HRMS (ESI) calcd for  $\text{C}_{21}\text{H}_{18}\text{F}_2\text{N}_5\text{O}$   $[\text{M} + \text{H}]^+$  394.1474, found 394.1469.

2-(4-氟苯基)-5-(1-(6-氟喹啉-4-基)哌啶-4-基)-1,3,4-噁二唑(**6f**): 白色固体, 收率 55.8%. m.p. 195~196 °C;  $^1\text{H}$  NMR (400 MHz,  $\text{DMSO}-d_6$ )  $\delta$ : 8.67 (s, 1H), 8.10~8.05 (m, 2H), 7.92 (dd,  $J=8.0, 4.0$  Hz, 1H), 7.80~7.72 (m, 2H), 7.49~7.43 (m, 2H), 4.26 (d,  $J=16.0$  Hz, 2H), 3.52~3.40 (m, 3H), 2.27~2.23 (m, 2H), 2.11~2.01 (m, 2H);  $^{13}\text{C}$  NMR (100 MHz,  $\text{DMSO}-d_6$ )  $\delta$ : 168.6, 164.1

(d,  $^1J_{\text{C-F}}=249.0$  Hz), 163.8 (d,  $^4J_{\text{C-F}}=4.0$  Hz), 163.2, 158.6 (d,  $^1J_{\text{C-F}}=243.0$  Hz), 153.3 (d,  $^4J_{\text{C-F}}=2.0$  Hz), 148.5, 131.0 (d,  $^3J_{\text{C-F}}=9.0$  Hz), 129.2 (d,  $^3J_{\text{C-F}}=9.0$  Hz), 122.5 (d,  $^2J_{\text{C-F}}=25.0$  Hz), 120.2 (d,  $^4J_{\text{C-F}}=3.0$  Hz), 116.7 (d,  $^2J_{\text{C-F}}=22.0$  Hz), 116.6 (d,  $^3J_{\text{C-F}}=8.0$  Hz), 109.4 (d,  $^2J_{\text{C-F}}=23.0$  Hz), 48.4, 32.4, 28.6; HRMS (ESI) calcd for  $\text{C}_{21}\text{H}_{18}\text{F}_2\text{N}_5\text{O}$   $[\text{M} + \text{H}]^+$  394.1474, found 394.1467.

2-(2-氯苯基)-5-(1-(6-氟喹啉-4-基)哌啶-4-基)-1,3,4-噁二唑(**6g**): 淡黄色固体, 收率 60.4%. m.p. 163~164 °C;  $^1\text{H}$  NMR (400 MHz,  $\text{DMSO}-d_6$ )  $\delta$ : 8.67 (s, 1H), 8.00 (dd,  $J=8.0, 4.0$  Hz, 1H), 7.92 (dd,  $J=8.0, 4.0$  Hz, 1H), 7.80~7.71 (m, 3H), 7.66 (td,  $J=8.0, 4.0$  Hz, 1H), 7.58 (td,  $J=8.0, 4.0$  Hz, 1H), 4.26 (d,  $J=12.0$  Hz, 2H), 3.55~3.49 (m, 1H), 3.47~3.40 (m, 2H), 2.28~2.24 (m, 2H), 2.11~2.02 (m, 2H);  $^{13}\text{C}$  NMR (100 MHz,  $\text{DMSO}-d_6$ )  $\delta$ : 169.0, 163.8 (d,  $^4J_{\text{C-F}}=4.0$  Hz), 162.1, 158.6 (d,  $^1J_{\text{C-F}}=244.0$  Hz), 153.3 (d,  $^4J_{\text{C-F}}=2.0$  Hz), 148.4, 133.2, 131.8, 131.3, 131.1, 131.0 (d,  $^3J_{\text{C-F}}=9.0$  Hz), 127.9, 122.8, 122.5 (d,  $^2J_{\text{C-F}}=25.0$  Hz), 116.6 (d,  $^3J_{\text{C-F}}=8.0$  Hz), 109.4 (d,  $^2J_{\text{C-F}}=23.0$  Hz), 48.4, 32.4, 28.6; HRMS (ESI) calcd for  $\text{C}_{21}\text{H}_{18}\text{FCIN}_5\text{O}$   $[\text{M} + \text{H}]^+$  410.1178, found 410.1173.

2-(3-氯苯基)-5-(1-(6-氟喹啉-4-基)哌啶-4-基)-1,3,4-噁二唑(**6h**): 白色固体, 收率 82.6%. m.p. 159~160 °C;  $^1\text{H}$  NMR (400 MHz,  $\text{DMSO}-d_6$ )  $\delta$ : 8.67 (s, 1H), 8.03 (t,  $J=2.0$  Hz, 1H), 8.01~7.98 (m, 1H), 7.92 (dd,  $J=8.0, 4.0$  Hz, 1H), 7.80~7.70 (m, 3H), 7.64 (t,  $J=4.0$  Hz, 1H), 4.26 (d,  $J=16.0$  Hz, 2H), 3.53~3.40 (m, 3H), 2.28~2.24 (m, 2H), 2.12~2.02 (m, 2H);  $^{13}\text{C}$  NMR (100 MHz,  $\text{DMSO}-d_6$ )  $\delta$ : 169.0, 163.8 (d,  $^4J_{\text{C-F}}=4.0$  Hz), 162.8, 158.6 (d,  $^1J_{\text{C-F}}=244.0$  Hz), 153.3 (d,  $^4J_{\text{C-F}}=2.0$  Hz), 148.5, 134.1, 131.8, 131.5, 131.0 (d,  $^3J_{\text{C-F}}=9.0$  Hz), 126.1, 125.5, 125.3, 122.6 (d,  $^2J_{\text{C-F}}=25.0$  Hz), 116.6 (d,  $^3J_{\text{C-F}}=8.0$  Hz), 109.4 (d,  $^2J_{\text{C-F}}=23.0$  Hz), 48.4, 32.5, 28.6; HRMS (ESI) calcd for  $\text{C}_{21}\text{H}_{18}\text{FCIN}_5\text{O}$   $[\text{M} + \text{H}]^+$  410.1178, found 410.1177.

2-(4-氯苯基)-5-(1-(6-氟喹啉-4-基)哌啶-4-基)-1,3,4-噁二唑(**6i**): 白色固体, 收率 76.0%. m.p. 188~189 °C;  $^1\text{H}$  NMR (400 MHz,  $\text{DMSO}-d_6$ )  $\delta$ : 8.67 (s, 1H), 8.03 (d,  $J=8.0$  Hz, 2H), 7.92 (dd,  $J=8.0, 4.0$  Hz, 1H), 7.78 (dd,  $J=8.0, 4.0$  Hz, 1H), 7.76~7.72 (m, 1H), 7.68 (d,  $J=8.0$  Hz, 2H), 4.26 (d,  $J=12.0$  Hz, 2H), 3.53~3.47 (m, 1H), 3.46~3.40 (m, 2H), 2.27~2.23 (m, 2H), 2.11~2.01 (m, 2H);  $^{13}\text{C}$  NMR (100 MHz,  $\text{DMSO}-d_6$ )  $\delta$ : 168.8, 163.8 (d,  $^4J_{\text{C-F}}=4.0$  Hz), 163.2, 158.6 (d,  $^1J_{\text{C-F}}=244.0$  Hz), 153.3

(d,  $^4J_{\text{C-F}}=2.0$  Hz), 148.5, 136.6, 131.1 (d,  $^3J_{\text{C-F}}=9.0$  Hz), 129.6, 128.4, 122.6 (d,  $^2J_{\text{C-F}}=25.0$  Hz), 122.5, 116.6 (d,  $^3J_{\text{C-F}}=8.0$  Hz), 109.4 (d,  $^2J_{\text{C-F}}=23.0$  Hz), 48.4, 32.5, 28.6; HRMS (ESI) calcd for  $\text{C}_{21}\text{H}_{18}\text{FCIN}_5\text{O}$   $[\text{M}+\text{H}]^+$  410.1178, found 410.1170.

2-(2-溴苯基)-5-(1-(6-氟喹啉-4-基)哌啶-4-基)-1,3,4-噁二唑(**6j**): 白色固体, 收率 67.4%. m.p. 164~165 °C;  $^1\text{H}$  NMR (400 MHz,  $\text{DMSO}-d_6$ )  $\delta$ : 8.67 (s, 1H), 7.95~7.88 (m, 3H), 7.80~7.72 (m, 2H), 7.62 (td,  $J=8.0$ , 4.0 Hz, 1H), 7.57 (td,  $J=8.0$ , 4.0 Hz, 1H), 4.25 (d,  $J=16.0$  Hz, 2H), 3.54~3.41 (m, 3H), 2.28~2.24 (m, 2H), 2.11~2.01 (m, 2H);  $^{13}\text{C}$  NMR (100 MHz,  $\text{DMSO}-d_6$ )  $\delta$ : 169.0, 163.9 (d,  $^4J_{\text{C-F}}=5.0$  Hz), 162.8, 158.6 (d,  $^1J_{\text{C-F}}=244.0$  Hz), 153.3 (d,  $^4J_{\text{C-F}}=2.0$  Hz), 148.4, 134.3, 133.3, 131.8, 131.0 (d,  $^3J_{\text{C-F}}=8.0$  Hz), 128.3, 125.0, 122.6 (d,  $^2J_{\text{C-F}}=25.0$  Hz), 120.9, 116.6 (d,  $^3J_{\text{C-F}}=9.0$  Hz), 109.4 (d,  $^2J_{\text{C-F}}=23.0$  Hz), 48.4, 32.4, 28.6; HRMS (ESI) calcd for  $\text{C}_{21}\text{H}_{18}\text{FBrN}_5\text{O}$   $[\text{M}+\text{H}]^+$  454.0673, found 454.0673.

2-(3-溴苯基)-5-(1-(6-氟喹啉-4-基)哌啶-4-基)-1,3,4-噁二唑(**6k**): 淡黄色固体, 收率 76.2%. m.p. 150~151 °C;  $^1\text{H}$  NMR (400 MHz,  $\text{DMSO}-d_6$ )  $\delta$ : 8.67 (s, 1H), 8.16 (t,  $J=4.0$  Hz, 1H), 8.04~8.02 (m, 1H), 7.92 (dd,  $J=8.0$ , 4.0 Hz, 1H), 7.86~7.83 (m, 1H), 7.80~7.72 (m, 2H), 7.57 (t,  $J=8.0$  Hz, 1H), 4.26 (d,  $J=16.0$  Hz, 2H), 3.53~3.40 (m, 3H), 2.28~2.24 (m, 2H), 2.12~2.02 (m, 2H);  $^{13}\text{C}$  NMR (100 MHz,  $\text{DMSO}-d_6$ )  $\delta$ : 169.0, 163.8 (d,  $^4J_{\text{C-F}}=4.0$  Hz), 162.7, 158.6 (d,  $^1J_{\text{C-F}}=244.0$  Hz), 153.3 (d,  $^4J_{\text{C-F}}=2.0$  Hz), 148.5, 134.6, 131.7, 131.0 (d,  $^3J_{\text{C-F}}=8.0$  Hz), 128.9, 125.7, 125.6, 122.5 (d,  $^2J_{\text{C-F}}=25.0$  Hz), 122.4, 116.6 (d,  $^3J_{\text{C-F}}=9.0$  Hz), 109.4 (d,  $^2J_{\text{C-F}}=23.0$  Hz), 48.4, 32.5, 28.6; HRMS (ESI) calcd for  $\text{C}_{21}\text{H}_{18}\text{FBrN}_5\text{O}$   $[\text{M}+\text{H}]^+$  454.0673, found 454.0662.

2-(4-溴苯基)-5-(1-(6-氟喹啉-4-基)哌啶-4-基)-1,3,4-噁二唑(**6l**): 白色固体, 收率 81.6%. m.p. 182~183 °C;  $^1\text{H}$  NMR (400 MHz,  $\text{DMSO}-d_6$ )  $\delta$ : 8.66 (s, 1H), 7.95 (d,  $J=8.0$  Hz, 2H), 7.91 (dd,  $J=8.0$ , 4.0 Hz, 1H), 7.82 (d,  $J=8.0$  Hz, 2H), 7.79~7.72 (m, 2H), 4.26 (d,  $J=12.0$  Hz, 2H), 3.52~3.39 (m, 3H), 2.27~2.23 (m, 2H), 2.11~2.01 (m, 2H);  $^{13}\text{C}$  NMR (100 MHz,  $\text{DMSO}-d_6$ )  $\delta$ : 168.8, 163.8 (d,  $^4J_{\text{C-F}}=4.0$  Hz), 163.3, 158.6 (d,  $^1J_{\text{C-F}}=243.0$  Hz), 153.3 (d,  $^4J_{\text{C-F}}=2.0$  Hz), 148.4, 132.5, 131.0 (d,  $^3J_{\text{C-F}}=9.0$  Hz), 128.5, 125.5, 122.8, 122.5 (d,  $^2J_{\text{C-F}}=25.0$  Hz), 116.6 (d,  $^3J_{\text{C-F}}=8.0$  Hz), 109.4 (d,  $^2J_{\text{C-F}}=23.0$  Hz), 48.4, 32.4, 28.6; HRMS (ESI) calcd for  $\text{C}_{21}\text{H}_{18}\text{FBrN}_5\text{O}$   $[\text{M}+\text{H}]^+$  454.0673, found 454.0662.

2-(1-(6-氟喹啉-4-基)哌啶-4-基)-5-(2-硝基苯基)-1,3,4-噁二唑(**6m**): 淡黄色固体, 收率 66.2%. m.p. 185~186 °C;  $^1\text{H}$  NMR (400 MHz,  $\text{DMSO}-d_6$ )  $\delta$ : 8.67 (s, 1H), 8.21~8.19 (m, 1H), 8.09~8.07 (m, 1H), 7.98~7.90 (m, 3H), 7.80~7.71 (m, 2H), 4.24 (d,  $J=12.0$  Hz, 2H), 3.55~3.48 (m, 1H), 3.47~3.40 (m, 2H), 2.24~2.20 (m, 2H), 2.07~1.98 (m, 2H);  $^{13}\text{C}$  NMR (100 MHz,  $\text{DMSO}-d_6$ )  $\delta$ : 169.5, 163.9 (d,  $^4J_{\text{C-F}}=4.0$  Hz), 160.6, 158.6 (d,  $^1J_{\text{C-F}}=243.0$  Hz), 153.3 (d,  $^4J_{\text{C-F}}=2.0$  Hz), 148.4, 147.89, 133.8, 133.4, 131.2, 131.0 (d,  $^3J_{\text{C-F}}=9.0$  Hz), 124.8, 122.5 (d,  $^2J_{\text{C-F}}=25.0$  Hz), 117.2, 116.6 (d,  $^3J_{\text{C-F}}=9.0$  Hz), 109.4 (d,  $^2J_{\text{C-F}}=23.0$  Hz), 48.3, 32.3, 28.5; HRMS (ESI) calcd for  $\text{C}_{21}\text{H}_{18}\text{FN}_6\text{O}_3$   $[\text{M}+\text{H}]^+$  421.1419, found 421.1411.

2-(1-(6-氟喹啉-4-基)哌啶-4-基)-5-(3-硝基苯基)-1,3,4-噁二唑(**6n**): 浅白色固体, 收率 70.1%. m.p. 154~155 °C;  $^1\text{H}$  NMR (400 MHz,  $\text{DMSO}-d_6$ )  $\delta$ : 8.67 (t,  $J=4.0$  Hz, 1H), 8.66 (s, 1H), 8.47~8.42 (m, 2H), 7.90 (dd,  $J=8.0$ , 4.0 Hz, 2H), 7.79~7.71 (m, 2H), 4.26 (d,  $J=12.0$  Hz, 2H), 3.56~3.48 (m, 1H), 3.47~3.40 (m, 2H), 2.30~2.26 (m, 2H), 2.13~2.04 (m, 2H);  $^{13}\text{C}$  NMR (100 MHz,  $\text{DMSO}-d_6$ )  $\delta$ : 169.3, 163.8 (d,  $^4J_{\text{C-F}}=5.0$  Hz), 162.5, 158.6 (d,  $^1J_{\text{C-F}}=243.0$  Hz), 153.3 (d,  $^4J_{\text{C-F}}=2.0$  Hz), 148.4, 148.2, 132.6, 131.4, 131.0 (d,  $^3J_{\text{C-F}}=8.0$  Hz), 126.3, 125.0, 122.5 (d,  $^2J_{\text{C-F}}=24.0$  Hz), 121.0, 116.6 (d,  $^3J_{\text{C-F}}=9.0$  Hz), 109.4 (d,  $^2J_{\text{C-F}}=23.0$  Hz), 48.4, 32.5, 28.6; HRMS (ESI) calcd for  $\text{C}_{21}\text{H}_{18}\text{FN}_6\text{O}_3$   $[\text{M}+\text{H}]^+$  421.1419, found 421.1411.

2-(1-(6-氟喹啉-4-基)哌啶-4-基)-5-(4-硝基苯基)-1,3,4-噁二唑(**6o**): 淡黄色固体, 收率 65.7%. m.p. 188~190 °C;  $^1\text{H}$  NMR (400 MHz,  $\text{DMSO}-d_6$ )  $\delta$ : 8.66 (s, 1H), 8.42 (d,  $J=12.0$  Hz, 2H), 8.26 (d,  $J=8.0$  Hz, 2H), 7.90 (dd,  $J=8.0$ , 4.0 Hz, 1H), 7.79~7.70 (m, 2H), 4.26 (d,  $J=16.0$  Hz, 2H), 3.56~3.49 (m, 1H), 3.47~3.40 (m, 2H), 2.29~2.25 (m, 2H), 2.13~2.03 (m, 2H);  $^{13}\text{C}$  NMR (100 MHz,  $\text{DMSO}-d_6$ )  $\delta$ : 169.5, 163.8 (d,  $^4J_{\text{C-F}}=5.0$  Hz), 162.6, 158.6 (d,  $^1J_{\text{C-F}}=244.0$  Hz), 153.3 (d,  $^4J_{\text{C-F}}=2.0$  Hz), 149.1, 148.4, 131.0 (d,  $^3J_{\text{C-F}}=8.0$  Hz), 129.1, 127.9, 124.6, 122.5 (d,  $^2J_{\text{C-F}}=25.0$  Hz), 116.6 (d,  $^3J_{\text{C-F}}=9.0$  Hz), 109.4 (d,  $^2J_{\text{C-F}}=23.0$  Hz), 48.4, 32.5, 28.6; HRMS (ESI) calcd for  $\text{C}_{21}\text{H}_{18}\text{FN}_6\text{O}_3$   $[\text{M}+\text{H}]^+$  421.1419, found 421.1405.

2-(1-(6-氟喹啉-4-基)哌啶-4-基)-5-(4-(三氟甲基)苯基)-1,3,4-噁二唑(**6p**): 白色固体, 收率 85.5%. m.p. 170~171 °C;  $^1\text{H}$  NMR (400 MHz,  $\text{DMSO}-d_6$ )  $\delta$ : 8.66 (s, 1H), 8.23 (d,  $J=8.0$  Hz, 2H), 7.98 (d,  $J=8.0$  Hz, 2H), 7.92 (dd,  $J=8.0$ , 4.0 Hz, 1H), 7.79~7.71 (m, 2H), 4.26 (d,  $J=$

12.0 Hz, 2H), 3.55~3.49 (m, 1H), 3.47~3.40 (m, 2H), 2.29~2.25 (m, 2H), 2.12~2.03 (m, 2H);  $^{13}\text{C}$  NMR (100 MHz, DMSO- $d_6$ )  $\delta$ : 169.7, 164.3 (d,  $^4J_{\text{C-F}}=5.0$  Hz), 163.4, 159.0 (d,  $^1J_{\text{C-F}}=244.0$  Hz), 153.7 (d,  $^4J_{\text{C-F}}=2.0$  Hz), 148.9, 131.9 (q,  $^2J_{\text{C-F}}=32.0$  Hz), 131.5 (d,  $^3J_{\text{C-F}}=9.0$  Hz), 127.8, 127.7, 126.8 (q,  $^3J_{\text{C-F}}=4.0$  Hz), 124.2 (q,  $^1J_{\text{C-F}}=271.0$  Hz), 122.9 (d,  $^2J_{\text{C-F}}=25.0$  Hz), 117.0 (d,  $^3J_{\text{C-F}}=8.0$  Hz), 109.8 (d,  $^2J_{\text{C-F}}=23.0$  Hz), 48.8, 32.9, 29.0; HRMS (ESI) calcd for  $\text{C}_{22}\text{H}_{18}\text{F}_4\text{N}_5\text{O}$   $[\text{M}+\text{H}]^+$  444.1442, found 444.1429.

4-(5-(1-(6-氟喹啉-4-基)哌啶-4-基)-1,3,4-噁二唑-2-基)氟基苯(**6q**): 黄色固体, 收率 72.9%. m.p. 183~184 °C;  $^1\text{H}$  NMR (400 MHz, DMSO- $d_6$ )  $\delta$ : 8.67 (s, 1H), 8.18 (d,  $J=12.0$  Hz, 2H), 8.08 (d,  $J=8.0$  Hz, 2H), 7.91 (dd,  $J=8.0, 4.0$  Hz, 1H), 7.79~7.70 (m, 2H), 4.26 (d,  $J=12.0$  Hz, 2H), 3.55~3.49 (m, 1H), 3.48~3.41 (m, 2H), 2.29~2.25 (m, 2H), 2.13~2.03 (m, 2H);  $^{13}\text{C}$  NMR (100 MHz, DMSO- $d_6$ )  $\delta$ : 169.3, 163.8 (d,  $^4J_{\text{C-F}}=5.0$  Hz), 162.8, 158.6 (d,  $^1J_{\text{C-F}}=244.0$  Hz), 153.3 (d,  $^4J_{\text{C-F}}=2.0$  Hz), 148.4, 133.4, 131.0 (d,  $^3J_{\text{C-F}}=9.0$  Hz), 127.5, 127.2, 122.5 (d,  $^2J_{\text{C-F}}=24.0$  Hz), 118.1, 116.6 (d,  $^3J_{\text{C-F}}=9.0$  Hz), 114.0, 109.4 (d,  $^2J_{\text{C-F}}=24.0$  Hz), 48.4, 32.5, 28.6; HRMS (ESI) calcd for  $\text{C}_{22}\text{H}_{18}\text{FN}_6\text{O}$   $[\text{M}+\text{H}]^+$  401.1521, found 401.1509.

2-(1-(6-氟喹啉-4-基)哌啶-4-基)-5-(4-甲氧基苯基)-1,3,4-噁二唑(**6r**): 白色固体, 收率 70.5%. m.p. 165~166 °C;  $^1\text{H}$  NMR (400 MHz, DMSO- $d_6$ )  $\delta$ : 8.67 (s, 1H), 7.95 (d,  $J=8.0, 2\text{H}$ ), 7.92 (dd,  $J=8.0, 4.0$  Hz, 1H), 7.80~7.72 (m, 2H), 7.14 (d,  $J=8.0$  Hz, 2H), 4.26 (d,  $J=12.0$  Hz, 2H), 3.85 (s, 3H), 3.49~3.39 (m, 3H), 2.26~2.22 (m, 2H), 2.10~2.00 (m, 2H);  $^{13}\text{C}$  NMR (100 MHz, DMSO- $d_6$ )  $\delta$ : 168.0, 163.9 (d,  $^4J_{\text{C-F}}=4.0$  Hz), 163.8, 161.9, 158.6 (d,  $^1J_{\text{C-F}}=244.0$  Hz), 153.3 (d,  $^4J_{\text{C-F}}=1.0$  Hz), 148.5, 131.0 (d,  $^3J_{\text{C-F}}=9.0$  Hz), 128.3, 122.6 (d,  $^2J_{\text{C-F}}=25.0$  Hz), 116.6 (d,  $^3J_{\text{C-F}}=9.0$  Hz), 115.9, 114.9, 109.4 (d,  $^2J_{\text{C-F}}=23.0$  Hz), 55.5, 48.5, 32.4, 28.7; HRMS (ESI) calcd for  $\text{C}_{22}\text{H}_{21}\text{FN}_5\text{O}_2$   $[\text{M}+\text{H}]^+$  406.1674, found 406.1662.

2-(1-(6-氟喹啉-4-基)哌啶-4-基)-5-(4-(三氟甲氧基)苯基)-1,3,4-噁二唑(**6s**): 白色固体, 收率 78.3%. m.p. 123~124 °C;  $^1\text{H}$  NMR (400 MHz, DMSO- $d_6$ )  $\delta$ : 8.68 (s, 1H), 8.15 (d,  $J=8.0$  Hz, 2H), 7.92 (dd,  $J=8.0, 4.0$  Hz, 1H), 7.80~7.71 (m, 2H), 7.61 (d,  $J=8.0$  Hz, 2H), 4.27 (d,  $J=16.0$  Hz, 2H), 3.54~3.41 (m, 3H), 2.29~2.25 (m, 2H), 2.12~2.03 (m, 2H);  $^{13}\text{C}$  NMR (100 MHz, DMSO- $d_6$ )  $\delta$ : 168.9, 163.8 (d,  $^4J_{\text{C-F}}=5.0$  Hz), 163.0, 158.6 (d,  $^1J_{\text{C-F}}=244.0$  Hz), 153.3 (d,  $^4J_{\text{C-F}}=2.0$  Hz), 150.5, 148.4, 131.1 (d,  $^3J_{\text{C-F}}=9.0$  Hz), 128.9, 122.7, 122.5 (d,  $^2J_{\text{C-F}}=25.0$  Hz),

121.8, 120.0 (q,  $^1J_{\text{C-F}}=256.0$  Hz), 116.6 (d,  $^3J_{\text{C-F}}=8.0$  Hz), 109.4 (d,  $^2J_{\text{C-F}}=23.0$  Hz), 48.4, 32.5, 28.6; HRMS (ESI) calcd for  $\text{C}_{22}\text{H}_{18}\text{F}_4\text{N}_5\text{O}_2$   $[\text{M}+\text{H}]^+$  460.1391, found 460.1379.

2-(1-(6-氟喹啉-4-基)哌啶-4-基)-5-(吡啶-2-基)-1,3,4-噁二唑(**6t**): 白色固体, 收率 90.6%. m.p. 215~216 °C;  $^1\text{H}$  NMR (400 MHz, DMSO- $d_6$ )  $\delta$ : 8.78 (d,  $J=4.0$  Hz, 1H), 8.67 (s, 1H), 8.19 (d,  $J=8.0$  Hz, 1H), 8.07 (td,  $J=8.0, 2.0$  Hz, 1H), 7.92 (dd,  $J=8.0, 4.0$  Hz, 1H), 7.80~7.73 (m, 2H), 7.65 (dd,  $J=8.0, 4.0$  Hz, 1H), 4.27 (d,  $J=16.0$  Hz, 2H), 3.57~3.45 (m, 3H), 2.27~2.24 (m, 2H), 2.11~2.02 (m, 2H);  $^{13}\text{C}$  NMR (100 MHz, DMSO- $d_6$ )  $\delta$ : 169.4, 163.8 (d,  $^4J_{\text{C-F}}=4.0$  Hz), 163.5, 158.6 (d,  $^1J_{\text{C-F}}=244.0$  Hz), 153.3 (d,  $^4J_{\text{C-F}}=2.0$  Hz), 150.3, 148.4, 142.9, 138.0, 131.0 (d,  $^3J_{\text{C-F}}=9.0$  Hz), 126.4, 122.9, 122.5 (d,  $^2J_{\text{C-F}}=25.0$  Hz), 116.6 (d,  $^3J_{\text{C-F}}=8.0$  Hz), 109.4 (d,  $^2J_{\text{C-F}}=23.0$  Hz), 48.4, 32.5, 28.6; HRMS (ESI) calcd for  $\text{C}_{20}\text{H}_{18}\text{FN}_6\text{O}$   $[\text{M}+\text{H}]^+$  377.1521, found 377.1514.

2-(1-(6-氟喹啉-4-基)哌啶-4-基)-5-(噻吩-2-基)-1,3,4-噁二唑(**6u**): 淡黄色固体, 收率 68.2%. m.p. 156~157 °C;  $^1\text{H}$  NMR (400 MHz, DMSO- $d_6$ )  $\delta$ : 8.67 (s, 1H), 7.95 (dd,  $J=4.0, 1.0$  Hz, 1H), 7.92 (dd,  $J=8.0, 4.0$  Hz, 1H), 7.83 (dd,  $J=4.0, 1.0$  Hz, 1H), 7.80~7.71 (m, 2H), 7.30 (dd,  $J=8.0, 4.0$  Hz, 1H), 4.26 (d,  $J=12.0$  Hz, 2H), 3.50~3.39 (m, 3H), 2.26~2.22 (m, 2H), 2.09~2.00 (m, 2H);  $^{13}\text{C}$  NMR (100 MHz, DMSO- $d_6$ )  $\delta$ : 168.0, 163.8 (d,  $^4J_{\text{C-F}}=5.0$  Hz), 160.2, 158.6 (d,  $^1J_{\text{C-F}}=243.0$  Hz), 153.3 (d,  $^4J_{\text{C-F}}=2.0$  Hz), 148.4, 131.4, 131.0 (d,  $^3J_{\text{C-F}}=9.0$  Hz), 130.1, 128.7, 124.5, 122.5 (d,  $^2J_{\text{C-F}}=25.0$  Hz), 116.6 (d,  $^3J_{\text{C-F}}=9.0$  Hz), 109.4 (d,  $^2J_{\text{C-F}}=23.0$  Hz), 48.4, 32.4, 28.6; HRMS (ESI) calcd for  $\text{C}_{19}\text{H}_{17}\text{FN}_5\text{OS}$   $[\text{M}+\text{H}]^+$  382.1132, found 382.1119.

2-(1-(6-氟喹啉-4-基)哌啶-4-基)-5-(呋喃-2-基)-1,3,4-噁二唑(**6v**): 白色固体, 收率 82.5%. m.p. 142~143 °C;  $^1\text{H}$  NMR (400 MHz, DMSO- $d_6$ )  $\delta$ : 8.67 (s, 1H), 8.06 (d,  $J=2.0$  Hz, 1H), 7.92 (dd,  $J=8.0, 4.0$  Hz, 1H), 7.80~7.71 (m, 2H), 7.35 (d,  $J=2.0$  Hz, 1H), 6.81 (dd,  $J=4.0, 1.0$  Hz, 1H), 4.25 (d,  $J=12.0$  Hz, 2H), 3.51~3.39 (m, 3H), 2.25~2.21 (m, 2H), 2.09~1.99 (m, 2H);  $^{13}\text{C}$  NMR (100 MHz, DMSO- $d_6$ )  $\delta$ : 167.8, 163.8 (d,  $^4J_{\text{C-F}}=4.0$  Hz), 158.6 (d,  $^1J_{\text{C-F}}=244.0$  Hz), 156.9, 153.3 (d,  $^4J_{\text{C-F}}=1.0$  Hz), 148.4, 146.8, 138.7, 131.0 (d,  $^3J_{\text{C-F}}=9.0$  Hz), 122.5 (d,  $^2J_{\text{C-F}}=25.0$  Hz), 116.6 (d,  $^3J_{\text{C-F}}=8.0$  Hz), 114.3, 112.6, 109.4 (d,  $^2J_{\text{C-F}}=23.0$  Hz), 48.4, 32.3, 28.6; HRMS (ESI) calcd for  $\text{C}_{19}\text{H}_{17}\text{FN}_5\text{O}_2$   $[\text{M}+\text{H}]^+$  366.1361,

found 366.1350.

2-(4-(叔丁基)苯基)-5-(1-(6-氟喹啉-4-基)吡啶-4-基)-1,3,4-噁二唑(**6w**): 白色固体, 收率 56.9%. m.p. 179~180 °C;  $^1\text{H}$  NMR (400 MHz, DMSO- $d_6$ )  $\delta$ : 8.66 (s, 1H), 7.94~7.89 (m, 3H), 7.79~7.72 (m, 2H), 7.61 (d,  $J=8.0$  Hz, 2H), 4.26 (d,  $J=12.0$  Hz, 2H), 3.50~3.39 (m, 3H), 2.26~2.23 (m, 2H), 2.09~2.01 (m, 2H), 1.32 (s, 9H);  $^{13}\text{C}$  NMR (100 MHz, DMSO- $d_6$ )  $\delta$ : 168.4, 163.9, 163.8 (d,  $^4J_{\text{C-F}}=5.0$  Hz), 158.6 (d,  $^1J_{\text{C-F}}=244.0$  Hz), 154.8, 153.3 (d,  $^4J_{\text{C-F}}=1.0$  Hz), 148.5, 131.0 (d,  $^3J_{\text{C-F}}=9.0$  Hz), 126.4, 126.3, 122.5 (d,  $^2J_{\text{C-F}}=25.0$  Hz), 120.9, 116.6 (d,  $^3J_{\text{C-F}}=9.0$  Hz), 109.4 (d,  $^2J_{\text{C-F}}=23.0$  Hz), 48.5, 34.9, 32.5, 30.9, 28.7; HRMS (ESI) calcd for  $\text{C}_{25}\text{H}_{27}\text{FN}_5\text{O}$  [ $\text{M}+\text{H}$ ] $^+$  432.2194, found 432.2187.

2-(1-(6-氟喹啉-4-基)吡啶-4-基)-5-苯基-1,3,4-噁二唑(**6x**): 白色固体, 收率 67.8%. m.p. 185~186 °C;  $^1\text{H}$  NMR (400 MHz, DMSO- $d_6$ )  $\delta$ : 8.67 (s, 1H), 8.03~8.01 (m, 2H), 7.92 (dd,  $J=8.0, 4.0$  Hz, 1H), 7.80~7.72 (m, 2H), 7.66~7.58 (m, 3H), 4.26 (d,  $J=12.0$  Hz, 2H), 3.53~3.41 (m, 3H), 2.28~2.25 (m, 2H), 2.12~2.02 (m, 2H);  $^{13}\text{C}$  NMR (100 MHz, DMSO- $d_6$ )  $\delta$ : 168.6, 163.9, 163.8 (d,  $^4J_{\text{C-F}}=5.0$  Hz), 158.6 (d,  $^1J_{\text{C-F}}=244.0$  Hz), 153.3 (d,  $^4J_{\text{C-F}}=2.0$  Hz), 148.4, 131.9, 131.0 (d,  $^3J_{\text{C-F}}=8.0$  Hz), 129.5, 126.5, 123.6, 122.5 (d,  $^2J_{\text{C-F}}=25.0$  Hz), 116.6 (d,  $^3J_{\text{C-F}}=9.0$  Hz), 109.4 (d,  $^2J_{\text{C-F}}=23.0$  Hz), 48.4, 32.5, 28.6; HRMS (ESI) calcd for  $\text{C}_{21}\text{H}_{19}\text{FN}_5\text{O}$  [ $\text{M}+\text{H}$ ] $^+$  376.1568, found 376.1562.

2-(1-(6-氟喹啉-4-基)吡啶-4-基)-5-(2,3,4-三甲氧基苯基)-1,3,4-噁二唑(**6y**): 浅白色固体, 收率 60.9%. m.p. 141~142 °C;  $^1\text{H}$  NMR (400 MHz, DMSO- $d_6$ )  $\delta$ : 8.67 (s, 1H), 7.92 (dd,  $J=8.0, 4.0$  Hz, 1H), 7.80~7.72 (m, 2H), 7.61 (d,  $J=8.0$  Hz, 1H), 7.03 (d,  $J=8.0$  Hz, 1H), 4.25 (d,  $J=12.0$  Hz, 2H), 3.90 (s, 3H), 3.87 (s, 3H), 3.81 (s, 3H), 3.51~3.40 (m, 3H), 2.27~2.23 (m, 2H), 2.10~2.00 (m, 2H);  $^{13}\text{C}$  NMR (100 MHz, DMSO- $d_6$ )  $\delta$ : 168.1, 163.9 (d,  $^4J_{\text{C-F}}=4.0$  Hz), 162.3, 158.6 (d,  $^1J_{\text{C-F}}=244.0$  Hz), 156.4, 153.3 (d,  $^4J_{\text{C-F}}=2.0$  Hz), 152.0, 148.4, 142.6, 131.0 (d,  $^3J_{\text{C-F}}=9.0$  Hz), 124.7, 122.5 (d,  $^2J_{\text{C-F}}=25.0$  Hz), 116.6 (d,  $^3J_{\text{C-F}}=9.0$  Hz), 110.8, 109.4 (d,  $^2J_{\text{C-F}}=23.0$  Hz), 108.8, 61.6, 60.6, 56.2, 48.5, 32.4, 28.6; HRMS (ESI) calcd for  $\text{C}_{24}\text{H}_{25}\text{FN}_5\text{O}_4$  [ $\text{M}+\text{H}$ ] $^+$  466.1885, found 466.1879.

### 3.2.4 目标化合物 **8a~8y** 的合成

在 50 mL 圆底烧瓶中加入 1.23 mmol 双酰肼 **7**, 327 mg (1.47 mmol)  $\text{P}_2\text{S}_5$  和二甲苯(25 mL), 搅拌加热至回流反应 6~8 h, 减压脱溶, 用 10% NaOH 溶液洗涤, 抽滤,

滤饼用 DMF-EtOH 重结晶得目标化合物 **8a~8y**.

2-(1-(6-氟喹啉-4-基)吡啶-4-基)-5-(2-甲基)-1,3,4-噁二唑(**8a**): 黄色固体, 收率 70.8%. m.p. 121~123 °C;  $^1\text{H}$  NMR (400 MHz, DMSO- $d_6$ )  $\delta$ : 8.67 (s, 1H), 7.92 (dd,  $J=8.0, 4.0$  Hz, 1H), 7.80~7.73 (m, 2H), 7.70 (d,  $J=8.0$  Hz, 1H), 7.48~7.42 (m, 2H), 7.37 (td,  $J=8.0, 2.0$  Hz, 1H), 4.34 (d,  $J=12.0$  Hz, 2H), 3.69~3.62 (m, 1H), 3.42~3.37 (m, 2H), 2.52 (s, 3H), 2.30~2.27 (m, 2H), 2.11~2.01 (m, 2H);  $^{13}\text{C}$  NMR (100 MHz, DMSO- $d_6$ )  $\delta$ : 174.2, 166.6, 163.8 (d,  $^4J_{\text{C-F}}=4.0$  Hz), 158.6 (d,  $^1J_{\text{C-F}}=244.0$  Hz), 153.3 (d,  $^4J_{\text{C-F}}=2.0$  Hz), 148.5, 136.5, 131.6, 131.0 (d,  $^3J_{\text{C-F}}=8.0$  Hz), 130.5, 130.4, 129.0, 126.6, 122.5 (d,  $^2J_{\text{C-F}}=25.0$  Hz), 116.6 (d,  $^3J_{\text{C-F}}=9.0$  Hz), 109.4 (d,  $^2J_{\text{C-F}}=23.0$  Hz), 49.0, 37.1, 32.0, 21.1; HRMS (ESI) calcd for  $\text{C}_{22}\text{H}_{21}\text{FN}_5\text{S}$  [ $\text{M}+\text{H}$ ] $^+$  406.1496, found 406.1482.

2-(1-(6-氟喹啉-4-基)吡啶-4-基)-5-(3-甲基)-1,3,4-噁二唑(**8b**): 浅绿色固体, 收率 56.1%. m.p. 139~141 °C;  $^1\text{H}$  NMR (400 MHz, DMSO- $d_6$ )  $\delta$ : 8.67 (s, 1H), 7.91 (dd,  $J=8.0, 4.0$  Hz, 1H), 7.79~7.72 (m, 4H), 7.44 (t,  $J=8.0$  Hz, 1H), 7.38 (d,  $J=8.0$  Hz, 1H), 4.33 (d,  $J=12.0$  Hz, 2H), 3.67~3.59 (m, 1H), 3.41~3.37 (m, 2H), 2.40 (s, 3H), 2.28~2.25 (m, 2H), 2.08~1.98 (m, 2H);  $^{13}\text{C}$  NMR (100 MHz, DMSO- $d_6$ )  $\delta$ : 173.8, 167.6, 163.8 (d,  $^4J_{\text{C-F}}=4.0$  Hz), 158.6 (d,  $^1J_{\text{C-F}}=243.0$  Hz), 153.3 (d,  $^4J_{\text{C-F}}=2.0$  Hz), 148.5, 139.0, 131.9, 131.0 (d,  $^3J_{\text{C-F}}=8.0$  Hz), 129.7, 129.4, 128.0, 124.8, 122.5 (d,  $^2J_{\text{C-F}}=24.0$  Hz), 116.6 (d,  $^3J_{\text{C-F}}=9.0$  Hz), 109.5 (d,  $^2J_{\text{C-F}}=23.0$  Hz), 49.0, 37.2, 32.0, 20.9; HRMS (ESI) calcd for  $\text{C}_{22}\text{H}_{21}\text{FN}_5\text{S}$  [ $\text{M}+\text{H}$ ] $^+$  406.1496, found 406.1488.

2-(1-(6-氟喹啉-4-基)吡啶-4-基)-5-(4-甲基)-1,3,4-噁二唑(**8c**): 浅黄色固体, 收率 74.2%. m.p. 125~126 °C;  $^1\text{H}$  NMR (400 MHz, DMSO- $d_6$ )  $\delta$ : 8.67 (s, 1H), 7.92 (dd,  $J=8.0, 4.0$  Hz, 1H), 7.85 (d,  $J=8.0$  Hz, 2H), 7.80~7.73 (m, 2H), 7.36 (d,  $J=8.0$  Hz, 2H), 4.33 (d,  $J=16.0$  Hz, 2H), 3.66~3.59 (m, 1H), 3.41~3.35 (m, 2H), 2.38 (s, 3H), 2.28~2.24 (m, 2H), 2.08~1.98 (m, 2H);  $^{13}\text{C}$  NMR (100 MHz, DMSO- $d_6$ )  $\delta$ : 173.5, 167.5, 163.8 (d,  $^4J_{\text{C-F}}=5.0$  Hz), 158.6 (d,  $^1J_{\text{C-F}}=244.0$  Hz), 153.3 (d,  $^4J_{\text{C-F}}=2.0$  Hz), 148.5, 141.3, 131.1 (d,  $^3J_{\text{C-F}}=8.0$  Hz), 130.1, 127.5, 127.1, 122.5 (d,  $^2J_{\text{C-F}}=25.0$  Hz), 116.6 (d,  $^3J_{\text{C-F}}=9.0$  Hz), 109.5 (d,  $^2J_{\text{C-F}}=23.0$  Hz), 49.0, 37.2, 32.0, 21.1; HRMS (ESI) calcd for  $\text{C}_{22}\text{H}_{21}\text{FN}_5\text{S}$  [ $\text{M}+\text{H}$ ] $^+$  406.1496, found 406.1487.

2-(2-氟苯基)-5-(1-(6-氟喹啉-4-基)吡啶-4-基)-1,3,4-噁二唑(**8d**): 浅黄色固体, 收率 56.8%. m.p.

169~170 °C;  $^1\text{H}$  NMR (400 MHz, DMSO- $d_6$ )  $\delta$ : 8.67 (s, 1H), 8.26 (td,  $J=8.0, 2.0$  Hz, 1H), 7.92 (dd,  $J=8.0, 4.0$  Hz, 1H), 7.80~7.75 (m, 2H), 7.69~7.63 (m, 1H), 7.53~7.48 (m, 1H), 7.45 (td,  $J=8.0, 2.0$  Hz, 1H), 4.34 (d,  $J=16.0$  Hz, 2H), 3.72~3.65 (m, 1H), 3.41~3.38 (m, 2H), 2.30~2.27 (m, 2H), 2.12~2.03 (m, 2H);  $^{13}\text{C}$  NMR (100 MHz, DMSO- $d_6$ )  $\delta$ : 175.0 (d,  $^4J_{\text{C-F}}=4.0$  Hz), 163.9 (d,  $^4J_{\text{C-F}}=4.0$  Hz), 159.7 (d,  $^2J_{\text{C-F}}=32.0$  Hz), 158.8 (d,  $^1J_{\text{C-F}}=248.0$  Hz), 158.6 (d,  $^1J_{\text{C-F}}=243.0$  Hz), 153.3 (d,  $^4J_{\text{C-F}}=2.0$  Hz), 148.5, 133.3 (d,  $^3J_{\text{C-F}}=8.0$  Hz), 131.0 (d,  $^3J_{\text{C-F}}=9.0$  Hz), 128.6, 125.6 (d,  $^4J_{\text{C-F}}=3.0$  Hz), 122.5 (d,  $^2J_{\text{C-F}}=24.0$  Hz), 117.6 (d,  $^3J_{\text{C-F}}=11.0$  Hz), 116.7 (d,  $^2J_{\text{C-F}}=22.0$  Hz), 116.6 (d,  $^3J_{\text{C-F}}=8.0$  Hz), 109.5 (d,  $^2J_{\text{C-F}}=23.0$  Hz), 49.0, 37.0, 32.0; HRMS (ESI) calcd for  $\text{C}_{21}\text{H}_{18}\text{F}_2\text{N}_5\text{S} [\text{M}+\text{H}]^+$  410.1246, found 410.1237.

2-(3-氟苯基)-5-(1-(6-氟喹啉-4-基)哌啶-4-基)-1,3,4-噻二唑(**8e**): 浅绿色固体, 收率 70.3%. m.p. 193~194 °C;  $^1\text{H}$  NMR (400 MHz, DMSO- $d_6$ )  $\delta$ : 8.67 (s, 1H), 7.92 (dd,  $J=8.0, 4.0$  Hz, 1H), 7.81~7.79 (m, 2H), 7.75 (td,  $J=8.0, 4.0$  Hz, 2H), 7.61 (dd,  $J=8.0, 4.0$  Hz, 1H), 7.45 (td,  $J=8.0, 4.0$  Hz, 1H), 4.34 (d,  $J=12.0$  Hz, 2H), 3.70~3.62 (m, 1H), 3.42~3.39 (m, 2H), 2.29~2.26 (m, 2H), 2.09~1.99 (m, 2H);  $^{13}\text{C}$  NMR (100 MHz, DMSO- $d_6$ )  $\delta$ : 174.6 (d,  $^4J_{\text{C-F}}=3.0$  Hz), 166.2 (d,  $^4J_{\text{C-F}}=3.0$  Hz), 163.8 (d,  $^4J_{\text{C-F}}=4.0$  Hz), 162.4 (d,  $^1J_{\text{C-F}}=248.0$  Hz), 158.6 (d,  $^1J_{\text{C-F}}=244.0$  Hz), 153.3 (d,  $^4J_{\text{C-F}}=2.0$  Hz), 148.5, 131.8 (d,  $^3J_{\text{C-F}}=8.0$  Hz), 131.7 (d,  $^3J_{\text{C-F}}=8.0$  Hz), 131.0 (d,  $^3J_{\text{C-F}}=9.0$  Hz), 124.0, 122.5 (d,  $^2J_{\text{C-F}}=25.0$  Hz), 118.1 (d,  $^2J_{\text{C-F}}=21.0$  Hz), 116.6 (d,  $^3J_{\text{C-F}}=9.0$  Hz), 114.1 (d,  $^2J_{\text{C-F}}=28.0$  Hz), 109.4 (d,  $^2J_{\text{C-F}}=23.0$  Hz), 48.9, 37.2, 32.0; HRMS (ESI) calcd for  $\text{C}_{21}\text{H}_{18}\text{F}_2\text{N}_5\text{S} [\text{M}+\text{H}]^+$  410.1246, found 410.1231.

2-(4-氟苯基)-5-(1-(6-氟喹啉-4-基)哌啶-4-基)-1,3,4-噻二唑(**8f**): 黄色固体, 收率 80.4%. m.p. 171~172 °C;  $^1\text{H}$  NMR (400 MHz, DMSO- $d_6$ )  $\delta$ : 8.68 (s, 1H), 8.05~8.01 (m, 2H), 7.92 (dd,  $J=8.0, 4.0$  Hz, 1H), 7.81~7.74 (m, 2H), 7.44~7.39 (m, 2H), 4.34 (d,  $J=12.0$  Hz, 2H), 3.69~3.61 (m, 1H), 3.42~3.36 (m, 2H), 2.28~2.25 (m, 2H), 2.09~1.99 (m, 2H);  $^{13}\text{C}$  NMR (100 MHz, DMSO- $d_6$ )  $\delta$ : 174.0, 166.4, 163.8 (d,  $^4J_{\text{C-F}}=4.0$  Hz), 163.7 (d,  $^1J_{\text{C-F}}=248.0$  Hz), 158.6 (d,  $^1J_{\text{C-F}}=244.0$  Hz), 153.3 (d,  $^4J_{\text{C-F}}=2.0$  Hz), 148.3, 130.9 (d,  $^3J_{\text{C-F}}=9.0$  Hz), 131.0 (d,  $^3J_{\text{C-F}}=9.0$  Hz), 126.4 (d,  $^4J_{\text{C-F}}=3.0$  Hz), 122.6 (d,  $^2J_{\text{C-F}}=25.0$  Hz), 116.7 (d,  $^2J_{\text{C-F}}=23.0$  Hz), 116.6, 109.5 (d,  $^2J_{\text{C-F}}=23.0$  Hz), 49.0, 37.2, 32.0; HRMS (ESI) calcd for

$\text{C}_{21}\text{H}_{18}\text{F}_2\text{N}_5\text{S} [\text{M}+\text{H}]^+$  410.1246, found 410.1236.

2-(2-氯苯基)-5-(1-(6-氟喹啉-4-基)哌啶-4-基)-1,3,4-噻二唑(**8g**): 白色固体, 收率 81.6%. m.p. 155~156 °C;  $^1\text{H}$  NMR (400 MHz, DMSO- $d_6$ )  $\delta$ : 8.67 (s, 1H), 8.14 (dd,  $J=8.0, 2.0$  Hz, 1H), 7.92 (dd,  $J=8.0, 4.0$  Hz, 1H), 7.80~7.75 (m, 2H), 7.72 (dd,  $J=8.0, 2.0$  Hz, 1H), 7.61 (td,  $J=8.0, 2.0$  Hz, 1H), 7.56 (td,  $J=8.0, 2.0$  Hz, 1H), 4.34 (d,  $J=12.0$  Hz, 2H), 3.73~3.65 (m, 1H), 3.41~3.36 (m, 2H), 2.31~2.27 (m, 2H), 2.13~2.03 (m, 2H);  $^{13}\text{C}$  NMR (100 MHz, DMSO- $d_6$ )  $\delta$ : 175.3, 163.8 (d,  $^4J_{\text{C-F}}=4.0$  Hz), 162.8, 158.6 (d,  $^1J_{\text{C-F}}=244.0$  Hz), 153.3 (d,  $^4J_{\text{C-F}}=2.0$  Hz), 148.5, 132.4, 131.5, 131.1, 131.0 (d,  $^3J_{\text{C-F}}=9.0$  Hz), 130.7, 128.5, 128.1, 122.5 (d,  $^2J_{\text{C-F}}=25.0$  Hz), 116.6 (d,  $^3J_{\text{C-F}}=8.0$  Hz), 109.5 (d,  $^2J_{\text{C-F}}=23.0$  Hz), 49.0, 37.0, 32.0; HRMS (ESI) calcd for  $\text{C}_{21}\text{H}_{18}\text{FCIN}_5\text{S} [\text{M}+\text{H}]^+$  426.0950, found 426.0939.

2-(3-氯苯基)-5-(1-(6-氟喹啉-4-基)哌啶-4-基)-1,3,4-噻二唑(**8h**): 浅黄色固体, 收率 78.5%. m.p. 168~169 °C;  $^1\text{H}$  NMR (400 MHz, DMSO- $d_6$ )  $\delta$ : 8.67 (s, 1H), 8.01 (t,  $J=2.0$  Hz, 1H), 7.93~7.90 (m, 2H), 7.80~7.73 (m, 2H), 7.66~7.64 (m, 1H), 7.59 (t,  $J=8.0$  Hz, 1H), 4.34 (d,  $J=12.0$  Hz, 2H), 3.70~3.63 (m, 1H), 3.42~3.36 (m, 2H), 2.28~2.26 (s, 2H), 2.09~1.99 (m, 2H);  $^{13}\text{C}$  NMR (100 MHz, DMSO- $d_6$ )  $\delta$ : 174.6, 166.1, 163.8 (d,  $^4J_{\text{C-F}}=4.0$  Hz), 158.6 (d,  $^1J_{\text{C-F}}=244.0$  Hz), 153.3 (d,  $^4J_{\text{C-F}}=2.0$  Hz), 148.4, 134.1, 131.6, 131.4, 131.0, 130.9 (d,  $^3J_{\text{C-F}}=9.0$  Hz), 126.8, 126.5, 122.5 (d,  $^2J_{\text{C-F}}=25.0$  Hz), 116.6 (d,  $^3J_{\text{C-F}}=9.0$  Hz), 109.5 (d,  $^2J_{\text{C-F}}=23.0$  Hz), 48.9, 37.2, 32.0; HRMS (ESI) calcd for  $\text{C}_{21}\text{H}_{18}\text{FCIN}_5\text{S} [\text{M}+\text{H}]^+$  426.0950, found 426.0939.

2-(4-氯苯基)-5-(1-(6-氟喹啉-4-基)哌啶-4-基)-1,3,4-噻二唑(**8i**): 浅绿色固体, 收率 89.1%. m.p. 171~172 °C;  $^1\text{H}$  NMR (400 MHz, DMSO- $d_6$ )  $\delta$ : 8.67 (s, 1H), 7.99 (d,  $J=8.0$  Hz, 2H), 7.92 (dd,  $J=8.0, 4.0$  Hz, 1H), 7.80~7.74 (m, 2H), 7.64 (d,  $J=8.0$  Hz, 2H), 4.34 (d,  $J=12.0$  Hz, 2H), 3.69~3.62 (m, 1H), 3.43~3.38 (m, 2H), 2.28~2.25 (m, 2H), 2.09~1.99 (m, 2H);  $^{13}\text{C}$  NMR (100 MHz, DMSO- $d_6$ )  $\delta$ : 174.3, 166.4, 163.8 (d,  $^4J_{\text{C-F}}=4.0$  Hz), 158.6 (d,  $^1J_{\text{C-F}}=244.0$  Hz), 153.3 (d,  $^4J_{\text{C-F}}=2.0$  Hz), 148.5, 135.9, 131.1 (d,  $^3J_{\text{C-F}}=8.0$  Hz), 129.6, 129.3, 128.6, 122.6 (d,  $^2J_{\text{C-F}}=25.0$  Hz), 116.6 (d,  $^3J_{\text{C-F}}=8.0$  Hz), 109.5 (d,  $^2J_{\text{C-F}}=24.0$  Hz), 49.0, 37.2, 32.0; HRMS (ESI) calcd for  $\text{C}_{21}\text{H}_{18}\text{FCIN}_5\text{S} [\text{M}+\text{H}]^+$  426.0950, found 426.0940.

2-(2-溴苯基)-5-(1-(6-氟喹啉-4-基)哌啶-4-基)-1,3,4-噻二唑(**8j**): 黄色固体, 收率 73.0%. m.p. 145~

146 °C;  $^1\text{H}$  NMR (400 MHz,  $\text{DMSO}-d_6$ )  $\delta$ : 8.67 (s, 1H), 7.99 (dd,  $J=8.0, 2.0$  Hz, 1H), 7.92 (dd,  $J=8.0, 4.0$  Hz, 1H), 7.87 (dd,  $J=8.0, 4.0$  Hz, 1H), 7.80~7.74 (m, 2H), 7.59 (td,  $J=8.0, 2.0$  Hz, 1H), 7.52 (td,  $J=8.0, 4.0$  Hz, 1H), 4.35 (d,  $J=12.0$  Hz, 2H), 3.73~3.65 (m, 1H), 3.41~3.35 (m, 2H), 2.31~2.28 (m, 2H), 2.12~2.02 (m, 2H);  $^{13}\text{C}$  NMR (100 MHz,  $\text{DMSO}-d_6$ )  $\delta$ : 175.2, 164.4, 163.9 (d,  $^4J_{\text{C-F}}=4.0$  Hz), 158.6 (d,  $^1J_{\text{C-F}}=244.0$  Hz), 153.3 (d,  $^4J_{\text{C-F}}=2.0$  Hz), 148.5, 134.0, 132.5, 131.8, 131.0 (d,  $^3J_{\text{C-F}}=9.0$  Hz), 130.5, 128.4, 122.5 (d,  $^2J_{\text{C-F}}=25.0$  Hz), 121.7, 116.6 (d,  $^3J_{\text{C-F}}=9.0$  Hz), 109.5 (d,  $^2J_{\text{C-F}}=23.0$  Hz), 49.0, 37.1, 32.0; HRMS (ESI) calcd for  $\text{C}_{21}\text{H}_{18}\text{FBrN}_5\text{S}$   $[\text{M}+\text{H}]^+$  470.0445, found 470.0432.

2-(3-溴苯基)-5-(1-(6-氟喹啉-4-基)哌啶-4-基)-1,3,4-噻二唑(**8k**): 浅黄色固体, 收率 54.5%. m.p. 166~167 °C;  $^1\text{H}$  NMR (400 MHz,  $\text{DMSO}-d_6$ )  $\delta$ : 8.67 (s, 1H), 8.15 (t,  $J=2.0$  Hz, 1H), 7.97~7.95 (m, 1H), 7.92 (dd,  $J=8.0, 4.0$  Hz, 1H), 7.80~7.73 (m, 3H), 7.53 (t,  $J=8.0$  Hz, 1H), 4.34 (d,  $J=16.0$  Hz, 2H), 3.70~3.63 (m, 1H), 3.43~3.35 (m, 2H), 2.29~2.25 (m, 2H), 2.09~1.99 (m, 2H);  $^{13}\text{C}$  NMR (100 MHz,  $\text{DMSO}-d_6$ )  $\delta$ : 174.6, 166.0, 163.8 (d,  $^4J_{\text{C-F}}=5.0$  Hz), 158.6 (d,  $^1J_{\text{C-F}}=243.0$  Hz), 153.3 (d,  $^4J_{\text{C-F}}=2.0$  Hz), 148.5, 133.9, 131.8, 131.7, 131.0 (d,  $^3J_{\text{C-F}}=9.0$  Hz), 129.6, 126.9, 122.6 (d,  $^2J_{\text{C-F}}=24.0$  Hz), 122.5, 116.6 (d,  $^3J_{\text{C-F}}=9.0$  Hz), 109.5 (d,  $^2J_{\text{C-F}}=23.0$  Hz), 49.0, 37.2, 32.0; HRMS (ESI) calcd for  $\text{C}_{21}\text{H}_{18}\text{FBrN}_5\text{S}$   $[\text{M}+\text{H}]^+$  470.0445, found 470.0432.

2-(4-溴苯基)-5-(1-(6-氟喹啉-4-基)哌啶-4-基)-1,3,4-噻二唑(**8l**): 黄色固体, 收率 70.3%. m.p. 192~193 °C;  $^1\text{H}$  NMR (400 MHz,  $\text{DMSO}-d_6$ )  $\delta$ : 8.67 (s, 1H), 7.93~7.90 (m, 3H), 7.80~7.73 (m, 4H), 4.33 (d,  $J=12.0$  Hz, 2H), 3.68~3.61 (m, 1H), 3.41~3.38 (m, 2H), 2.28~2.25 (m, 2H), 2.09~1.99 (m, 2H);  $^{13}\text{C}$  NMR (100 MHz,  $\text{DMSO}-d_6$ )  $\delta$ : 174.3, 166.5, 163.8 (d,  $^4J_{\text{C-F}}=4.0$  Hz), 158.6 (d,  $^1J_{\text{C-F}}=244.0$  Hz), 153.3 (d,  $^4J_{\text{C-F}}=2.0$  Hz), 148.5, 132.5, 131.0 (d,  $^3J_{\text{C-F}}=9.0$  Hz), 129.5, 128.9, 124.7, 122.5 (d,  $^2J_{\text{C-F}}=25.0$  Hz), 116.6 (d,  $^3J_{\text{C-F}}=8.0$  Hz), 109.5 (d,  $^2J_{\text{C-F}}=23.0$  Hz), 48.9, 37.2, 32.0; HRMS (ESI) calcd for  $\text{C}_{21}\text{H}_{18}\text{FBrN}_5\text{S}$   $[\text{M}+\text{H}]^+$  470.0445, found 470.0432.

2-(1-(6-氟喹啉-4-基)哌啶-4-基)-5-(2-硝基苯基)-1,3,4-噻二唑(**8m**): 黄色固体, 收率 66.2%. m.p. 201~202 °C;  $^1\text{H}$  NMR (400 MHz,  $\text{DMSO}-d_6$ )  $\delta$ : 8.67 (s, 1H), 8.14~8.12 (m, 1H), 7.96~7.82 (m, 4H), 7.80~7.75 (m, 2H), 4.34 (d,  $J=16.0$  Hz, 2H), 3.72~3.66 (m, 1H), 3.41~3.35 (m, 2H), 2.30~2.27 (m, 2H), 2.11~2.01 (m,

2H);  $^{13}\text{C}$  NMR (100 MHz,  $\text{DMSO}-d_6$ )  $\delta$ : 175.8, 163.8 (d,  $^4J_{\text{C-F}}=4.0$  Hz), 162.5, 158.6 (d,  $^1J_{\text{C-F}}=243.0$  Hz), 153.3 (d,  $^4J_{\text{C-F}}=1.0$  Hz), 148.4, 148.3, 133.4, 132.4, 132.2, 131.0 (d,  $^3J_{\text{C-F}}=8.0$  Hz), 124.8, 123.1, 122.5 (d,  $^2J_{\text{C-F}}=25.0$  Hz), 116.6 (d,  $^3J_{\text{C-F}}=8.0$  Hz), 109.5 (d,  $^2J_{\text{C-F}}=23.0$  Hz), 49.0, 37.1, 32.0; HRMS (ESI) calcd for  $\text{C}_{21}\text{H}_{18}\text{FN}_6\text{O}_2\text{S}$   $[\text{M}+\text{H}]^+$  437.1191, found 437.1179.

2-(1-(6-氟喹啉-4-基)哌啶-4-基)-5-(3-硝基苯基)-1,3,4-噻二唑(**8n**): 黄色固体, 收率 78.0%. m.p. 205~207 °C;  $^1\text{H}$  NMR (400 MHz,  $\text{DMSO}-d_6$ )  $\delta$ : 8.70 (t,  $J=2.0$  Hz, 1H), 8.67 (s, 1H), 8.42~8.38 (m, 2H), 7.92 (dd,  $J=8.0, 4.0$  Hz, 1H), 7.86 (t,  $J=8.0$  Hz, 1H), 7.80~7.73 (m, 2H), 4.34 (d,  $J=12.0$  Hz, 2H), 3.73~3.66 (m, 1H), 3.44~3.40 (m, 2H), 2.30~2.27 (m, 2H), 2.11~2.01 (m, 2H);  $^{13}\text{C}$  NMR (100 MHz,  $\text{DMSO}-d_6$ )  $\delta$ : 175.1, 165.5, 163.8 (d,  $^4J_{\text{C-F}}=4.0$  Hz), 162.4, 158.6 (d,  $^1J_{\text{C-F}}=244.0$  Hz), 153.3 (d,  $^4J_{\text{C-F}}=1.0$  Hz), 148.5, 148.3, 134.0, 131.3, 131.0 (d,  $^3J_{\text{C-F}}=9.0$  Hz), 125.6, 122.5 (d,  $^2J_{\text{C-F}}=25.0$  Hz), 121.7, 116.6 (d,  $^3J_{\text{C-F}}=9.0$  Hz), 109.5 (d,  $^2J_{\text{C-F}}=23.0$  Hz), 48.9, 37.2, 32.0; HRMS (ESI) calcd for  $\text{C}_{21}\text{H}_{18}\text{FN}_6\text{O}_2\text{S}$   $[\text{M}+\text{H}]^+$  437.1191, found 437.1179.

2-(1-(6-氟喹啉-4-基)哌啶-4-基)-5-(4-硝基苯基)-1,3,4-噻二唑(**8o**): 红色固体, 收率 69.5%. m.p. 224~226 °C;  $^1\text{H}$  NMR (400 MHz,  $\text{DMSO}-d_6$ )  $\delta$ : 8.67 (s, 1H), 8.39 (d,  $J=12.0$  Hz, 2H), 8.25 (d,  $J=12.0$  Hz, 2H), 7.92 (dd,  $J=8.0, 4.0$  Hz, 1H), 7.80~7.73 (m, 2H), 4.34 (d,  $J=12.0$  Hz, 2H), 3.74~3.66 (m, 1H), 3.46~3.39 (m, 2H), 2.30~2.27 (m, 2H), 2.11~2.01 (m, 2H);  $^{13}\text{C}$  NMR (100 MHz,  $\text{DMSO}-d_6$ )  $\delta$ : 175.6, 165.6, 163.8 (d,  $^4J_{\text{C-F}}=5.0$  Hz), 162.3, 158.6 (d,  $^1J_{\text{C-F}}=244.0$  Hz), 153.3 (d,  $^4J_{\text{C-F}}=1.0$  Hz), 148.7, 148.5, 131.0 (d,  $^3J_{\text{C-F}}=9.0$  Hz), 128.8, 124.7, 122.5 (d,  $^2J_{\text{C-F}}=25.0$  Hz), 116.6 (d,  $^3J_{\text{C-F}}=9.0$  Hz), 109.5 (d,  $^2J_{\text{C-F}}=23.0$  Hz), 48.9, 37.2, 32.0; HRMS (ESI) calcd for  $\text{C}_{21}\text{H}_{18}\text{FN}_6\text{O}_2\text{S}$   $[\text{M}+\text{H}]^+$  437.1191, found 437.1174.

2-(1-(6-氟喹啉-4-基)哌啶-4-基)-5-(4-(三氟甲基)苯基)-1,3,4-噻二唑(**8p**): 浅绿色固体, 收率 85.2%. m.p. 191~192 °C;  $^1\text{H}$  NMR (400 MHz,  $\text{DMSO}-d_6$ )  $\delta$ : 8.67 (s, 1H), 8.19 (d,  $J=8.0$  Hz, 2H), 7.93 (d,  $J=8.0$  Hz, 2H), 7.92 (dd,  $J=8.0, 4.0$  Hz, 1H), 7.80~7.73 (m, 2H), 4.34 (d,  $J=12.0$  Hz, 2H), 3.72~3.65 (m, 1H), 3.42~3.36 (m, 2H), 2.30~2.27 (m, 2H), 2.11~2.01 (m, 2H);  $^{13}\text{C}$  NMR (100 MHz,  $\text{DMSO}-d_6$ )  $\delta$ : 175.0, 166.1, 163.8 (d,  $^4J_{\text{C-F}}=5.0$  Hz), 158.6 (d,  $^1J_{\text{C-F}}=243.0$  Hz), 153.3 (d,  $^4J_{\text{C-F}}=2.0$  Hz), 148.5, 132.2 (q,  $^1J_{\text{C-F}}=270.0$  Hz), 131.0 (d,  $^3J_{\text{C-F}}=9.0$  Hz), 130.9 (q,  $^2J_{\text{C-F}}=32.0$  Hz), 130.7, 128.4, 126.4 (q,  $^3J_{\text{C-F}}=5.0$  Hz),

122.5 (d,  $^2J_{\text{C-F}}=25.0$  Hz), 116.6 (d,  $^3J_{\text{C-F}}=8.0$  Hz), 109.5 (d,  $^2J_{\text{C-F}}=22.0$  Hz), 48.9, 37.2, 32.0; HRMS (ESI) calcd for  $\text{C}_{22}\text{H}_{18}\text{F}_4\text{N}_5\text{S} [\text{M}+\text{H}]^+$  460.1214, found 460.1197.

2-(1-(6-氟喹啉-4-基)哌啶-4-基)-1,3,4-噻二唑-2-基)氰基苯(**8q**): 浅红色固体, 收率 72.4%. m.p. 194~196 °C;  $^1\text{H}$  NMR (400 MHz,  $\text{DMSO}-d_6$ )  $\delta$ : 8.67 (s, 1H), 8.15 (d,  $J=8.0$  Hz, 2H), 8.03 (d,  $J=8.0$  Hz, 2H), 7.91 (dd,  $J=8.0, 4.0$  Hz, 1H), 7.79~7.72 (m, 2H), 4.34 (d,  $J=12.0$  Hz, 2H), 3.72~3.64 (m, 1H), 3.42~3.36 (m, 2H), 2.30~2.26 (m, 2H), 2.10~2.00 (m, 2H);  $^{13}\text{C}$  NMR (100 MHz,  $\text{DMSO}-d_6$ )  $\delta$ : 175.3, 166.0, 163.8 (d,  $^4J_{\text{C-F}}=5.0$  Hz), 158.6 (d,  $^1J_{\text{C-F}}=244.0$  Hz), 153.3 (d,  $^4J_{\text{C-F}}=1.0$  Hz), 148.4, 133.7, 133.4, 131.0 (d,  $^3J_{\text{C-F}}=9.0$  Hz), 128.3, 122.5 (d,  $^2J_{\text{C-F}}=25.0$  Hz), 118.3, 116.6 (d,  $^3J_{\text{C-F}}=8.0$  Hz), 113.4, 109.5 (d,  $^2J_{\text{C-F}}=23.0$  Hz), 48.9, 37.2, 32.0; HRMS (ESI) calcd for  $\text{C}_{22}\text{H}_{18}\text{FN}_6\text{S} [\text{M}+\text{H}]^+$  417.1292, found 417.1277.

2-(1-(6-氟喹啉-4-基)哌啶-4-基)-5-(4-甲氧基苯基)-1,3,4-噻二唑(**8r**): 白色固体, 收率 80.3%. m.p. 164~165 °C;  $^1\text{H}$  NMR (400 MHz,  $\text{DMSO}-d_6$ )  $\delta$ : 8.67 (s, 1H), 7.93~7.89 (m, 3H), 7.80~7.73 (m, 2H), 7.10 (d,  $J=8.0$  Hz, 2H), 4.33 (d,  $J=16.0$  Hz, 2H), 3.84 (s, 3H), 3.63~3.59 (m, 1H), 3.41~3.36 (m, 2H), 2.26~2.23 (m, 2H), 2.07~1.97 (m, 2H);  $^{13}\text{C}$  NMR (100 MHz,  $\text{DMSO}-d_6$ )  $\delta$ : 172.9, 167.2, 163.8 (d,  $^4J_{\text{C-F}}=4.0$  Hz), 161.5, 158.6 (d,  $^1J_{\text{C-F}}=244.0$  Hz), 153.3 (d,  $^4J_{\text{C-F}}=2.0$  Hz), 148.5, 131.0 (d,  $^3J_{\text{C-F}}=9.0$  Hz), 129.2, 122.5 (d,  $^2J_{\text{C-F}}=25.0$  Hz), 122.3, 116.6 (d,  $^3J_{\text{C-F}}=9.0$  Hz), 114.8, 109.5 (d,  $^2J_{\text{C-F}}=23.0$  Hz), 55.5, 49.0, 37.1, 32.0; HRMS (ESI) calcd for  $\text{C}_{22}\text{H}_{21}\text{FN}_5\text{OS} [\text{M}+\text{H}]^+$  422.1445, found 422.1430.

2-(1-(6-氟喹啉-4-基)哌啶-4-基)-5-(4-(三氟甲氧基)苯基)-1,3,4-噻二唑(**8s**): 浅白色固体, 收率 75.5%. m.p. 170~171 °C;  $^1\text{H}$  NMR (400 MHz,  $\text{DMSO}-d_6$ )  $\delta$ : 8.67 (s, 1H), 8.11 (d,  $J=8.0$  Hz, 2H), 7.92 (dd,  $J=8.0, 4.0$  Hz, 1H), 7.80~7.73 (m, 2H), 7.56 (d,  $J=8.0$  Hz, 2H), 4.34 (d,  $J=12.0$  Hz, 2H), 3.70~3.62 (m, 1H), 3.42~3.35 (m, 2H), 2.29~2.26 (m, 2H), 2.10~2.00 (m, 2H);  $^{13}\text{C}$  NMR (100 MHz,  $\text{DMSO}-d_6$ )  $\delta$ : 174.5, 166.1, 163.8 (d,  $^4J_{\text{C-F}}=4.0$  Hz), 158.6 (d,  $^1J_{\text{C-F}}=244.0$  Hz), 153.3 (d,  $^4J_{\text{C-F}}=2.0$  Hz), 150.1, 148.5, 131.0 (d,  $^3J_{\text{C-F}}=8.0$  Hz), 129.7, 128.9, 122.5 (d,  $^2J_{\text{C-F}}=25.0$  Hz), 121.9, 120.0 (q,  $^1J_{\text{C-F}}=255.0$  Hz), 116.6 (d,  $^3J_{\text{C-F}}=8.0$  Hz), 109.5 (d,  $^2J_{\text{C-F}}=23.0$  Hz), 48.9, 37.2, 32.0; HRMS (ESI) calcd for  $\text{C}_{22}\text{H}_{18}\text{F}_4\text{N}_5\text{OS} [\text{M}+\text{H}]^+$  476.1163, found 476.1149.

2-(1-(6-氟喹啉-4-基)哌啶-4-基)-5-(吡啶-2-

基)-1,3,4-噻二唑(**8t**): 浅灰色固体, 收率 81.7%. m.p. 194~195 °C;  $^1\text{H}$  NMR (400 MHz,  $\text{DMSO}-d_6$ )  $\delta$ : 8.70 (d,  $J=8.0$  Hz, 1H), 8.66 (s, 1H), 8.25 (d,  $J=8.0$  Hz, 1H), 8.03 (td,  $J=8.0, 2.0$  Hz, 1H), 7.91 (dd,  $J=8.0, 4.0$  Hz, 1H), 7.79~7.72 (m, 2H), 7.59~7.56 (m, 1H), 4.33 (d,  $J=16.0$  Hz, 2H), 3.66~3.60 (m, 1H), 3.40~3.34 (m, 2H), 2.28~2.26 (m, 2H), 2.10~2.00 (m, 2H);  $^{13}\text{C}$  NMR (100 MHz,  $\text{DMSO}-d_6$ )  $\delta$ : 175.6, 169.5, 163.8 (d,  $^4J_{\text{C-F}}=4.0$  Hz), 158.6 (d,  $^1J_{\text{C-F}}=244.0$  Hz), 153.3 (d,  $^4J_{\text{C-F}}=1.0$  Hz), 150.2, 148.5, 148.3, 138.1, 131.0 (d,  $^3J_{\text{C-F}}=9.0$  Hz), 126.0, 122.5 (d,  $^2J_{\text{C-F}}=25.0$  Hz), 120.3, 116.6 (d,  $^3J_{\text{C-F}}=9.0$  Hz), 109.5 (d,  $^2J_{\text{C-F}}=23.0$  Hz), 49.0, 37.2, 32.0; HRMS (ESI) calcd for  $\text{C}_{20}\text{H}_{18}\text{FN}_6\text{S} [\text{M}+\text{H}]^+$  393.1292, found 393.1278.

2-(1-(6-氟喹啉-4-基)哌啶-4-基)-5-(噻吩-2-基)-1,3,4-噻二唑(**8u**): 浅黄色固体, 收率 57.3%. m.p. 165~166 °C;  $^1\text{H}$  NMR (400 MHz,  $\text{DMSO}-d_6$ )  $\delta$ : 8.67 (s, 1H), 7.91 (dd,  $J=8.0, 4.0$  Hz, 1H), 7.83 (d,  $J=4.0$  Hz, 1H), 7.77~7.73 (m, 3H), 7.24 (t,  $J=8.0, 4.0$  Hz, 1H), 4.33 (d,  $J=12.0$  Hz, 2H), 3.65~3.58 (m, 1H), 3.40~3.36 (m, 2H), 2.26~2.24 (m, 2H), 2.07~1.97 (m, 2H);  $^{13}\text{C}$  NMR (100 MHz,  $\text{DMSO}-d_6$ )  $\delta$ : 173.2, 163.8 (d,  $^4J_{\text{C-F}}=4.0$  Hz), 161.4, 158.6 (d,  $^1J_{\text{C-F}}=244.0$  Hz), 153.3 (d,  $^4J_{\text{C-F}}=2.0$  Hz), 148.4, 131.6, 131.0 (d,  $^3J_{\text{C-F}}=9.0$  Hz), 130.7, 130.3, 128.6, 122.5 (d,  $^2J_{\text{C-F}}=24.0$  Hz), 116.6 (d,  $^3J_{\text{C-F}}=9.0$  Hz), 109.5 (d,  $^2J_{\text{C-F}}=23.0$  Hz), 48.9, 37.1, 31.9; HRMS (ESI) calcd for  $\text{C}_{19}\text{H}_{17}\text{FN}_5\text{S}_2 [\text{M}+\text{H}]^+$  398.0904, found 398.0893.

2-(1-(6-氟喹啉-4-基)哌啶-4-基)-5-(呋喃-2-基)-1,3,4-噻二唑(**8v**): 浅黄色固体, 收率 52.0%. m.p. 148~149 °C;  $^1\text{H}$  NMR (400 MHz,  $\text{DMSO}-d_6$ )  $\delta$ : 8.66 (s, 1H), 8.00 (dd,  $J=4.0, 1.0$  Hz, 1H), 7.90 (dd,  $J=8.0, 4.0$  Hz, 1H), 7.78~7.71 (m, 2H), 7.28 (dd,  $J=2.0, 1.0$  Hz, 1H), 6.76 (dd,  $J=4.0, 2.0$  Hz, 1H), 4.32 (d,  $J=16.0$  Hz, 2H), 3.66~3.58 (m, 1H), 3.39~3.36 (m, 2H), 2.27~2.23 (m, 2H), 2.07~1.97 (m, 2H);  $^{13}\text{C}$  NMR (100 MHz,  $\text{DMSO}-d_6$ )  $\delta$ : 172.8, 163.8 (d,  $^4J_{\text{C-F}}=4.0$  Hz), 158.6 (d,  $^1J_{\text{C-F}}=244.0$  Hz), 157.6, 153.2 (d,  $^4J_{\text{C-F}}=2.0$  Hz), 148.3, 146.2, 144.7, 130.9 (d,  $^3J_{\text{C-F}}=8.0$  Hz), 122.5 (d,  $^2J_{\text{C-F}}=25.0$  Hz), 116.6 (d,  $^3J_{\text{C-F}}=9.0$  Hz), 112.9, 112.0, 109.5 (d,  $^2J_{\text{C-F}}=23.0$  Hz), 49.0, 37.0, 32.0; HRMS (ESI) calcd for  $\text{C}_{19}\text{H}_{17}\text{FN}_5\text{OS} [\text{M}+\text{H}]^+$  382.1132, found 382.1117.

2-(4-(叔丁基)苯基)-5-(1-(6-氟喹啉-4-基)哌啶-4-基)-1,3,4-噻二唑(**8w**): 浅黄色固体, 收率 67.1%. m.p. 158~159 °C;  $^1\text{H}$  NMR (400 MHz,  $\text{DMSO}-d_6$ )  $\delta$ : 8.67 (s, 1H), 7.92 (dd,  $J=8.0, 4.0$  Hz, 1H), 7.87 (d,  $J=8.0$  Hz, 2H), 7.79~7.73 (m, 2H), 7.57 (d,  $J=8.0$  Hz, 2H), 4.34 (d,

$J=13.0$  Hz, 2H), 3.66~3.59 (m, 1H), 3.50~3.41 (m, 2H), 2.27~2.24 (m, 2H), 2.08~1.98 (m, 2H), 1.31 (s, 9H);  $^{13}\text{C}$  NMR (100 MHz, DMSO- $d_6$ )  $\delta$ : 173.5, 167.4, 163.8 (d,  $^4J_{\text{C-F}}=4.0$  Hz), 158.6 (d,  $^1J_{\text{C-F}}=244.0$  Hz), 154.1, 153.3 (d,  $^4J_{\text{C-F}}=2.0$  Hz), 148.3, 131.0 (d,  $^3J_{\text{C-F}}=8.0$  Hz), 127.4, 127.1, 126.3, 122.6 (d,  $^2J_{\text{C-F}}=24.0$  Hz), 116.6 (d,  $^3J_{\text{C-F}}=9.0$  Hz), 109.5 (d,  $^2J_{\text{C-F}}=23.0$  Hz), 49.0, 37.2, 34.7, 32.0, 30.9; HRMS (ESI) calcd for  $\text{C}_{25}\text{H}_{27}\text{FN}_5\text{O}$   $[\text{M} + \text{H}]^+$  432.2194, found 432.2187.

2-(1-(6-氟喹啉-4-基)哌啶-4-基)-5-苯基-1,3,4-噻二唑(**8x**): 白色固体, 收率 70.6%. m.p. 181~182 °C;  $^1\text{H}$  NMR (400 MHz, DMSO- $d_6$ )  $\delta$ : 8.67 (s, 1H), 7.97 (dd,  $J=8.0, 4.0$  Hz, 2H), 7.92 (dd,  $J=8.0, 4.0$  Hz, 1H), 7.80~7.73 (m, 2H), 7.58~7.55 (m, 3H), 4.34 (d,  $J=12.0$  Hz, 2H), 3.68~3.60 (m, 1H), 3.41~3.37 (m, 2H), 2.28~2.26 (m, 2H), 2.09~1.99 (m, 2H);  $^{13}\text{C}$  NMR (100 MHz, DMSO- $d_6$ )  $\delta$ : 173.9, 167.5, 163.8 (d,  $^4J_{\text{C-F}}=4.0$  Hz), 158.6 (d,  $^1J_{\text{C-F}}=244.0$  Hz), 153.3 (d,  $^4J_{\text{C-F}}=2.0$  Hz), 148.5, 131.3, 131.0 (d,  $^3J_{\text{C-F}}=9.0$  Hz), 129.7, 129.5, 127.6, 122.5 (d,  $^2J_{\text{C-F}}=25.0$  Hz), 116.6 (d,  $^3J_{\text{C-F}}=9.0$  Hz), 109.5 (d,  $^2J_{\text{C-F}}=23.0$  Hz), 49.0, 37.2, 32.0; HRMS (ESI) calcd for  $\text{C}_{21}\text{H}_{19}\text{FN}_5\text{S}$   $[\text{M} + \text{H}]^+$  392.1340, found 392.1330.

2-(1-(6-氟喹啉-4-基)哌啶-4-基)-5-(3,4,5-三甲氧基苯基)-1,3,4-噻二唑(**8y**): 浅灰色固体, 收率 53.7%. m.p. 164~165 °C;  $^1\text{H}$  NMR (400 MHz, DMSO- $d_6$ )  $\delta$ : 8.67 (s, 1H), 7.91 (dd,  $J=8.0, 4.0$  Hz, 1H), 7.78~7.73 (m, 2H), 7.21 (s, 2H), 4.33 (d,  $J=12.0$  Hz, 2H), 3.88 (s, 6H), 3.73 (s, 3H), 3.66~3.60 (m, 1H), 3.41~3.36 (m, 2H), 2.27~2.24 (m, 2H), 2.06~1.98 (m, 2H);  $^{13}\text{C}$  NMR (100 MHz, DMSO- $d_6$ )  $\delta$ : 173.9, 167.4, 163.8 (d,  $^4J_{\text{C-F}}=4.0$  Hz), 158.6 (d,  $^1J_{\text{C-F}}=244.0$  Hz), 153.4, 153.3 (d,  $^4J_{\text{C-F}}=1.0$  Hz), 148.5, 139.8, 131.0 (d,  $^3J_{\text{C-F}}=9.0$  Hz), 125.1, 122.5 (d,  $^2J_{\text{C-F}}=25.0$  Hz), 116.6 (d,  $^3J_{\text{C-F}}=9.0$  Hz), 109.5 (d,  $^2J_{\text{C-F}}=23.0$  Hz), 104.9, 60.2, 56.2, 49.0, 37.2, 32.1; HRMS (ESI) calcd for  $\text{C}_{24}\text{H}_{25}\text{FN}_5\text{O}_3\text{S}$   $[\text{M} + \text{H}]^+$  482.1657, found 482.1640.

### 3.3 抑菌活性测试方法

#### 3.3.1 抗真菌活性测试方法

采用菌丝生长速率法<sup>[2,25]</sup>, 在马铃薯葡萄糖琼脂培养基(PDA)上测试目标化合物 **6a~6y** 和 **8a~8y** 对小麦赤霉病菌(*Gibberella zeae*)、油菜炭疽病菌(*Colletotrichum gloeosporioides*)和苹果腐烂病菌(*Cytospora mandshurica*)的体外抑制活性。普筛浓度均为 50  $\mu\text{g/mL}$ , 每个样品重复 3 次, 同时以商品化药剂噻霉灵(Hymexazol)为阳性对照药, 等量 DMSO 为空白对照。

沿培养的新鲜病原菌菌落边缘 3~4 mm 处打取直径为 4 mm 的菌饼, 反向移接到培养皿中央位置, 然后置于  $(28 \pm 1)$  °C 培养箱中培养 3~5 d, 待空白对照菌落直径生长至接近培养皿直径的 2/3 时, 采用十字交叉法测出相应菌落直径, 按下式计算所测目标化合物的抑制率。

$$\text{抑制率}(\%) = (C - T) / (C - 0.4) \times 100\%$$

其中,  $C$  为空白对照组的菌落直径,  $T$  为加药试验组的菌落直径。

#### 3.3.2 抗细菌活性测试方法

采用浊度法<sup>[5,25]</sup>, 以水稻白叶枯病菌(*Xoo*)、柑橘溃疡病菌(*Xac*)和烟草青枯病菌(*Rs*)为测试对象, 以商品化杀菌剂叶枯唑(BMT)和噻菌铜(TDC)为阳性对照药剂。初筛浓度分别为 100 和 50  $\mu\text{g/mL}$ , 测试了化合物 **6a~6y** 和 **8a~8y** 的体外抗细菌活性。将样品和对照药剂分别配置成浓度为 100 和 50  $\mu\text{g/mL}$  的含毒 NB 液体培养基于试管中, 测定其 OD 值, 该值即为无菌培养基 OD 值。然后接入受试细菌, 在  $(28 \pm 1)$  °C、180 r/min 的恒温摇床上振荡培养 48 h, 将两个浓度的菌液在分光光度计上测定 OD 值, 该值即为含菌培养基的 OD 值。按下式计算所测化合物的抑制率。

校正 OD 值 = 含菌培养基 OD 值 - 无菌培养基 OD 值

$$\text{抑制率}(\%) = (\text{校正后对照培养基菌液 OD 值} - \text{校正后含毒培养基 OD 值}) / \text{校正后对照培养基菌液 OD 值} \times 100\%$$

**辅助材料 (Supporting Information)** 目标化合物 **6i** 和 **8x** 的晶体学数据, 中间体 **7a~7y**、目标化合物 **6a~6y** 及 **8a~8y** 的  $^1\text{H}$  NMR、 $^{13}\text{C}$  NMR 和 HRMS 原始谱图。这些材料可以免费从本刊网站(<http://sioc-journal.cn/>)上下载。

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