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Development of a Synthesis For a Long-Term Oxazolidinone Antibacterial

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Abstract:

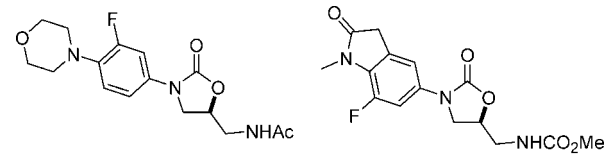
Linezolid, compound 1, is a member of the oxazolidinone class of antibacterials and has had recent clinical interest due to its potential use as a long-term treatment for bacterial infection. Detailed herein are improvements to the original synthesis to enable phase I clinical trials. Of particular interest is the preparation of a key oxindole subunit utilizing a Pd-mediated cyclization. Optimization of the synthesis of the oxindole included the use of trifluorotoluene as the solvent.

Introduction

The emergence of bacterial resistance to even the most effective antibiotics has renewed interest in developing therapeutics with novel modes of action.[1] Linezolid (Zyvox)[2] is the first of a structurally unique class of oxazolidinone antibiotics introduced in early 2000 (Figure 1).[3] Its mechanism of action involves binding to a ribosomal subunit, thus preventing bacterial protein synthesis.[4] Linezolid has efficacy against a broad range of Gram-positive bacteria, including those resistant to many current chemotherapeutics, such as vancomycin. While linezolid has a number of advantages, there are adverse affects such as myelotoxicity,[5] especially after extended regimens, and also potential monoamine oxidase inhibitor activity.[6] A goal of the long-term (LT) oxazolidinone program was development of a compound with improved safety to enable extended treatment of chronic bacterial infections. To further the progression of this candidate, a scale-up synthesis amenable to delivering kilogram quantities, potentially into phase II trials, was developed.

Results and Discussion

Earlier candidates containing the oxindole core were prepared by the nitration of an appropriately substituted monofluorophenylacetic acid. Scheme 1 shows the route to **1** utilized by Discovery Chemistry[7] beginning with the nitration of a difluorinated substrate **2** leading to methyl oxindole **5**. This optimized reaction gave regioisomers **3a**,**b** as a 1:1 mixture. Fluoride displacement with methylamine led to isomers **4a**,**b**, which were easily separated upon conversion to oxindole **5**. While adequate for providing for SAR activities, the phenylacetic acid **2** proved difficult to source as well, requiring an undesirable and unselective nitration. Requirements for increasing amounts of **1** necessitated exploration of alternative chemistry to provide an adequate supply of the desired oxindole intermediate.



Linezolid 1

Figure 1. **Oxazolidinone antibacterials linezolid (Zyvox), 1.**

Recently, several palladium-mediated methods for the preparation of oxindoles have been reported (Scheme 2). The method of Hartwig used an acylated orthobromoaniline,[8] while an alternative developed by Buchwald used a chloroacetanalide[9] in the oxindole cyclizations. The availability of starting materials as well as higher reported yields led to choosing the latter for the scale-up of **5**.

The preparation of chloroacetanilide **7** (Scheme 3) begins with 3,4-difluoronitrobenzene. Fluoride displacement with anhydrous methylamine was initially used but was hampered by formation of a difficult to stir mixture with a vigorous exotherm. A switch to 40% aqueous methylamine gave a dose-controlled reaction at 40 °C leading to a 99% yield of **6**. Acylation with chloroacetyl chloride in toluene at 90 °C led to a 95% yield of **7**. The two steps were telescoped by forming **6** in toluene which was then carried as a solution directly into the acylation step, following an aqueous extraction to remove fluoride salts. This combined process gave an 88% yield over two steps and was utilized to prepare more than 12 kg of **7**.

An initial attempt to cyclize **7** to **5** met with limited success with a moderate yield (~70%) and poor purity (85%) after preparative TLC isolation[7] on small scale. The initial conditions followed those previously reported[9] (80 °C in toluene with 1.5

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(1) Bush, K.; Macielag, M.; Weidner-Wells, M. *Curr. Opin. Microbiol.* **2004**, *7*, 466–476.

(2) Brickner, S. J.; Hutchinson, D. K.; Barbachyn, M. R.; Manninen, P. R.; Ulanowicz, D. A.; Garmon, S. A.; Grega, K. C.; Hendges, S. K.; Toops, D. S.; Ford, C. W.; Zurenko, G. E. *J. Med. Chem.* **1996**, *39*, 673–679.

(3) Wilcox, M. H. *Expert Opin. Pharmacother.* **2005**, *6*, 2315–2326.

(4) (a) Diekema, D. J.; Jones, R. N. *Lancet* **2001**, *358*, 1975–1982. (b) Aoki, H.; Ke, L.; Poppe, S. M.; Poel, T. J.; Weaver, E. A.; Gadwood, R. C.; Thomas, R. C.; Shinabarger, D. L.; Ganoza, M. C. *Antimicrob. Agents Chemother.* **2002**, *46*, 1080–1085.

(5) Waldrep, T. W.; Skiest, D. J. *Pharmacotherapy* **2002**, *22*, 109–112.

(6) Humphrey, S. J.; Curry, J. T.; Turman, C. N.; Stryd, R. P. *J. Cardiovasc. Pharmacol.* **2001**, *37*, 548–563.

(7) Grodeev, M. F.; Josyula, V. P. V. N.; Luehr, G. W. WO 2006/106427, 2006; CAN 145:419125.

(8) (a) Shaughnessy, K. H.; Hamann, B. C.; Hartwig, J. F. *J. Org. Chem.* **1998**, *63*, 6546–6553. (b) Lee, S.; Hartwig, J. F. *J. Org. Chem.* **2001**, *66*, 3402–3415.

(9) Hennessy, E. J.; Buchwald, S. L. *J. Am. Chem. Soc.* **2003**, *125*, 12084–12085.

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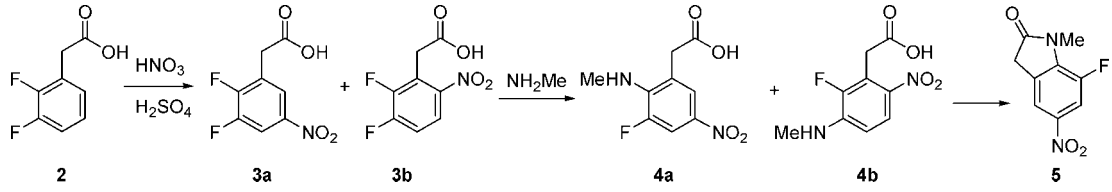
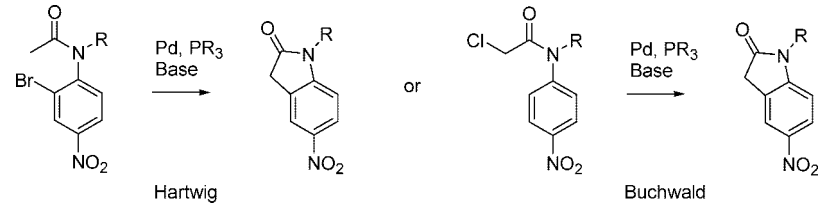
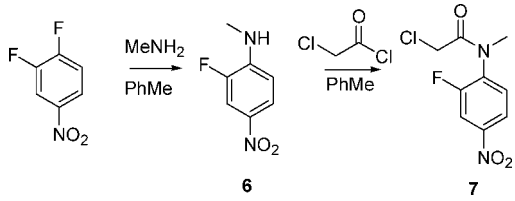
Scheme 1. **Nitration-based route to oxindole 5**



Scheme 2. **Hartwig/Buchwald palladium-catalyzed oxindole formations**



Scheme 3. **Preparation of choloracetanilide 7**



Scheme 4. **Preparation of oxindole 8**

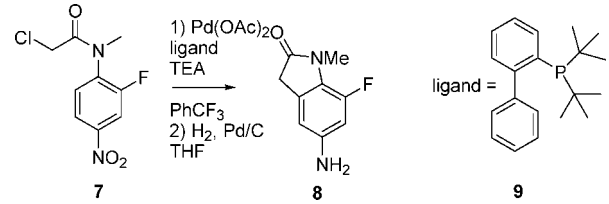


Table 1. **Comparison of solvents for use in palladium-catalyzed cyclization**

solvent	bp (°C)	polarity[a]	cost/L ($U.S.)[b]	HAP[c]
TFT	102	0.24	26.40	no
toluene	110	0.099	24.00	yes
DMF	153	0.386	43.00	yes
dioxane	100	0.164	42.40	yes

[a] Relative measure of solvent polarity.[11] [b] Comparison of the price per 1 L of >99% purity from Sigma-Aldrich. [c] EPA list of hazardous air pollutants (HAP).

equiv of triethylamine), but this unfortunately led to significant decomposition. Reducing the temperature led to an incomplete reaction, while extending the reaction time led to little improvement. A solvent screen was run comparing toluene to 2-methyltetrahydrofuran (MeTHF), trifluorotoluene (TFT),[10] DMF, and DME. Of these, TFT and DMF showed the most promise with >50% reaction at 55 °C after 3 h. When DMF was scaled to 10 g, complete conversion of starting material took place after 5 h but was accompanied by significant decomposition. One concern to address was the potential base sensitivity of **5**, especially at elevated temperatures. Indeed, treatment of **5** with triethylamine in DMF at 60 °C after 1 h shows a complex mixture by HPLC with the oxindole as less than 50%. By 5 h the oxindole had decreased to less than 20%. With this in mind we decided to examine TFT as the reaction solvent. While not commonly used on scale for pharmaceutical processing, TFT has merits which proved of interest in exploring its potential utility as a processing solvent (Table 1). Its reduced boiling point especially with regard to DMF has an advantage for performing solvent switches or concentrations. From an environmental perspective it is not listed as a hazardous air pollutant (HAP) by the U.S. EPA and unlike many halogenated solvents has not been implicated in ozone depletion. Comparison of cost shows it to be competitive with toluene and more economical than either DMF or dioxane. As a reaction solvent it has a relative polarity midway between those of dioxane and DMF while being much greater than that of toluene. With these considerations in mind we decided to further examine the utility of TFT for the optimization of the oxindole formation. Switching to TFT as the solvent gave complete reaction after 5 h and led to precipitation of the product as it was formed, thereby minimizing decomposition. The yield of **5** was typically ~75%. While this yield was considered adequate, further experimental efforts were spent in attempting to further optimize the reaction.

An attempt to increase the yield by using the more reactive bromoacetanilide to accelerate the putative rate-controlling step of palladium insertion gave no reaction. Confirming the initial observation by Buchwald that ligand **9** appears to be the only acceptable participant in the oxindole-forming reaction, attempts to use dicyclohexyl bisphenylphosphine[12] or P(*t*-Bu)$_3$HBF$_4$[13] failed to give more than trace amounts of the desired product. An attempt was also made to lower the catalyst loading from 3% Pd(OAc)$_2$ and 6% ligand to minimize the expense of ligand **9** but led to stalled conversion of less than 40%. Given the availability of **9** on kilogram scale, coupled with the issues related to scaling the phenylacetic acid route, and finally with the relatively moderate amounts of **1** needed for this stage of the program we decided to forego further attempts to optimize the reaction. Lack of solubility of **5** led to omitting an aqueous workup to remove contaminating salts and led to development

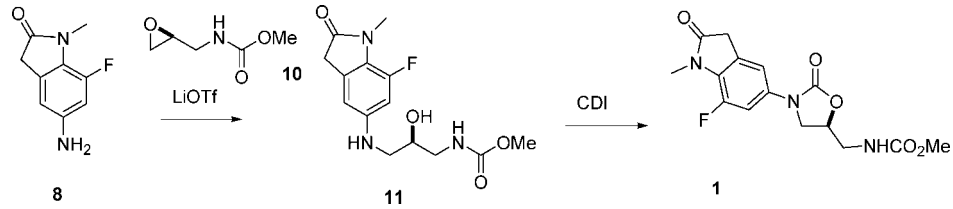
(10) For the use of TFT in process development see: Frampton, G. A.; Hannah, D. R.; Henderson, N.; Katz, R. B.; Smith, I. H.; Tremayne, N.; Watson, R. J.; Woollam, I. *Org Process Res. Dev.* **2004**, *8*, 415–417. (b) For some of the advantages of using TFT as a solvent see: Knochel, P.; Auge, J. *Modern Solvents in Organic Synthesis*; Springer-Verlag: Berlin, 1999.

(11) Reichardt, C. *Solvents and Solvent Effects in Organic Chemistry*; Wiley: Weinheim, 2003.

(12) Wolfe, J. P.; Singer, R. A.; Yang, B. H.; Buchwald, S. L. *J. Am. Chem. Soc.* **1999**, *121*, 9550–9561.

(13) Netherton, M. R.; Fu, G. C. *Org. Lett.* **2001**, *3*, 4295–4298.

Scheme 5. **Alkyation of aniline 8 and formation of oxazolidinone 1**



of a direct isolation. A solvent switch to isopropanol gave essentially complete precipitated oxindole along with triethylamine hydrochloride while removing the ligand and other impurities. Filtration was followed by an aqueous wash to remove the hydrochloride salt with the yield increasing from a typical laboratory scale of 75% to 86%, providing 4.9 kg of **5**.

Initially reduction of the nitro to the corresponding aniline with Raney Ni in THF gave **8** in a quantitative yield and 90% purity. To simplify the final metals analysis and in light of the relative base sensitivity of **5** a switch to Pd/C was examined. Indeed the purity improved to 95% with a quantitiative yield, while residual palladium carried through from the oxindole-forming reaction was reduced from 10,000 ppm in **5** to 150 ppm in **8**. Given the base sensitivity it was felt that the switch to Pd/C as the catalyst would prove to be even more important, given extended processing times. While the early isolation was accomplished by distilling to dryness, a method amenable to large scale was needed. It was found that isolating from a solution of THF/heptane further increased the purity to >98% while providing 2.7 kg (65% yield) of aniline **8**. The reduced yield was deemed acceptable at this point in development to ensure attaining final purity as the remaining two steps led to isolation of clinical API.

Alkylation of **8** with epoxide **10**[14] in the presence of stoichiometric lithium triflate in *t*-BuOH proved rather sluggish with typical reaction times of 48 h at 30 °C to reach >90% conversion with a ratio of 9:1 of mono- to dialkylation. Increased temperatures led to considerable amounts of the over-alkylated aniline as the major impurity which tended to be difficult to remove (~3:1 mono/di). The addition of MtBE as the antisolvent led to product precipitation which after filtration led to a reduction in the dialkylated impurity from ~10% to 1%. Further reaction optimization led to utilizing ethanol as the reaction solvent with an improvement to ~30:1 of mono- to dialkylated aniline. The improved ratio was maintained upon scale up; however, the reaction time extended to 144 h with multiple charges (twice with 0.4 kg) of **10** required to reach acceptable conversion. Why the reaction time became magnified is not understood although the need for the multiple charges is assumed to result from competitive epoxide opening by ethanol. After addition of MtBE and filtration the product was isolated in 68% yield (3.2 kg).

Oxazolidinone formation was accomplished by treatment with 1,1′-carbonyldiimidazole (CDI) in acetonitrile with the product precipitating from solution. The initial filtration gives product as the undesired anhydrous polymorph with ~1% imidazole but is necessary to reach the desired purity. Crystallization from acetonitrile/water removed the remaining imidazole leading to 3 kg of **1** in 77% yield and 99.9% purity as the correct polymorph.

(14) Perrault, W. R.; Pearlman, B. A.; Godrej, D. B.; Jeganathan, A.; Yamagata, K.; Chen, J. J.; Lu, C. V.; Herrinton, P. M.; Gadwood, R. C.; Chan, L.; Lyster, M. A.; Maloney, M. T.; Moeslein, J. A.; Green, M. L.; Barbachyn, M. R. *Org. Process Res. Dev.* **2003**, *7*, 533–546.

Conclusions

A kilogram-scale preparation of the oxazolidinone antibacterial **1** used a Pd-mediated cyclization to give a key oxindole intermediate. The synthesis gave an overall yield of 26% from 1,2-difluoronitrobenzene over a total of six linear steps. Hydrogenation of an aromatic nitro group utilized a strategic change of metal catalyst to simplify final metals analysis and to increase purity. The choice of TFT as the reaction solvent gave complete reaction at reduced temperature as well as precipitating the base-sensitive oxindole during the reaction. These conditions resulted in an improved yield and purity while eliminating the need for an untenable purification. Given the high catalyst loading, further optimization of the palladium cyclization is necessary but has proven to be amenable for kilogram scale for current deliveries. Finally, the choice of solvent proved necessary to suppress undesired over-alkylation to provide the penultimate product.

Experimental Section

All NMR spectra were obtained using a Varian 400 spectrometer. Chiral analysis was done using an Agilent 1100 HPLC with Chiral PAK AD, 250 mm × 4.6 mm, 10 μm, isocratic 60% hexanes/40% IPA for 16 min, 8 min equilibration, 20 °C, UV detection at 215 nm.

2-Chloro-*N*-(2-fluoro-4-nitrophenyl)-*N*-methylacetamide (7). A Hastelloy reactor was charged with 1,2-difluoronitrobenzene (9.3 kg, 58 mol) and toluene (47.7 kg) and was warmed to 40 °C. Methylamine, 40% aqueous (11.2 kg, 145 mol), was added in portions over 1 h; initially the reaction endothermed to 36 °C followed by an exotherm to 42 °C. The reaction was stirred at 40 °C for 20 h followed by heating to 60 °C to dissolve the formed solids. Stirring was ended, two layers formed, and the aqueous layer was removed. The organic layer was washed with water (10 kg) and then further diluted with toluene (7.7 kg). The organic layer was concentrated by distillation of approximately 10 L of toluene. The temperature was reduced to 85 °C, and chloroacetyl chloride (7.7 kg, 68 mol) was added at less than 90 °C. The resulting HCl gas was removed with a caustic scrubber. The mixture was held at 85 °C for 15 h followed by vacuum distillation to reach a volume of ~20 L. IPA (30 kg) was charged, and atmospheric distillation continued until a volume of ~20 L was reached. IPA (30 kg) was charged followed by cooling to 30 °C, and seed crystals (50 g) were added followed by a hold period until crystallization occurred. It was further cooled to 5 °C and the solid collected

by filtration. The filter cake was washed with isopropanol (7 kg) followed by drying at 60 °C under vacuum in a tray drier to yield 12.5 kg of **6** (88%). ^{1}H NMR (DMSO-d_6) δ 3.26 (s, 3 H), 4.33 (s, 2 H), 7.81 (s, 1 H) 8.14 (d, 1 H, J = 9.54), 8.28 (d, 1H, J = 9.54). ^{13}C NMR (DMSO-d_6) δ 166.49, 158.61, 156.08, 131.18, 121.17, 113.54, 113.28, 42.90, 37.57. Anal. Calcd for $C_9H_8ClFN_2O_3$: C, 43.83; H, 3.27; N, 11.36; F, 7.70. Found: C, 43.78; H, 3.32; N, 11.12; F, 7.62. MS m/z 247 (M^+).

7-Fluoro-1-methyl-5-nitro-1,3-dihydroindol-2-one (5). A Hastelloy reactor was charged with **6** (6.7 kg, 27.2 mol) followed by trifluorotoluene (60.7 kg) and triethylamine (2.8 kg, 27.7 mol). The stirring reaction was heated to 30 °C and then degassed three times with vacuum followed by nitrogen inertion. Palladium acetate (0.18 kg, 0.82 mol) and 2-(di-*tert*-butylphosphino)biphenyl (0.49 kg, 1.6 mol) were added, and the mixture was degassed an additional two times. The mixture was heated to an internal temperature of 55 °C for 6 h. The mixture was vacuum distilled to ~20 L followed by the addition of isopropanol (39 kg) and again concentrated to ~20 L. Cooling to 5 °C was followed by filtering and then washing with isopropanol (8 kg) and with water (22 kg). The resulting tan solid was dried at 50 °C under vacuum to afford 4.94 kg (87% yield) of **5**. ^{1}H NMR (DMSO, d_6) δ 3.3 (s, 2 H), 3.74 (s, 3 H), 8.1 (s, 1 H), 8.13 (d, 1 H, J = 1.2). ^{13}C NMR (DMSO-d_6) δ 175.16, 147.01, 144.58, 142.29, 129.21, 116.91, 113.47, 113.23, 36.08, 28.9. Anal. Calcd for $C_9H_7FN_2O_3$: C, 51.43; H, 3.36; N, 13.33; F, 9.04. Found: C, 51.36; H, 3.38; N, 12.85; F, 9.03. MS m/z 209 (M^-).

5-Amino-7-fluoro-1-methyl-1,3-dihydro-indol-2-one (8). A reactor was charged with 5% Pd/C (0.5 kg) followed by **5** (4.94 kg, 23.5 mol) and THF (68 kg). After several nitrogen purges and several hydrogen purges the contents of the reactor were heated to 40 °C at 65 PSIG for 20 h. After several nitrogen purges the catalyst was removed by filtration under nitrogen followed by washing with additional THF (37 kg). The solution of **8** was condensed to ~45 L by atmospheric distillation followed by cooling to 30 °C and holding until crystallization occurred. Heptane (16 kg) was added followed by cooling to 5 °C followed by filtering and rinsing with 1:1 THF/heptane (6 kg). The product was dried at 40 °C under vacuum to give 2.7 kg of **8** as a tan solid (65%). ^{1}H NMR (DMSO-d_6) δ 3.15 (s, 3 H), 3.43 (s, 2H), 5.05 (s broad, 2 H), 6.27 (d, 1 H, J = 13.9) and 6.34 (s, 1 H). ^{13}C NMR (DMSO-d_6) δ 173.81, 149.06, 146.70, 146.04, 129.02, 120.80, 107.91, 100.32, 100.10, 36.38, 28.68. Anal. Calcd for $C_9H_9FN_2O$: C, 59.99; H, 5.03; N, 15.55; F, 10.54. Found: C, 59.84; H, 4.76; N, 15.36; F, 10.15. MS m/z 181 (M^+).

(*R*)-[3-(7-Fluoro-1-methyl-2-oxo-2,3-dihydro-1H-indol-5-ylamino)-2-hydroxy-propyl]carbamic Acid Methyl Ester (11). A glass-lined reactor was charged with **8** (2.7 kg, 15 mol) and solid lithium triflate (2.4 kg, 15.4 mol) followed by the addition of ethanol (18.7 kg). The (*S*)-epoxide **10** (2.1 kg, 16 mol) was added, and the reaction mixture was allowed to stir at 35 °C for 168 h. Additional charges of **10** (0.4 kg, 3 mol) were made at 120 and 144 h, respectively. The reactor was charged with methyl *tert*-butyl ether (7.9 kg). The resulting fine slurry was cooled to 0 °C and held for 1 h followed by filtering and washing with additional methyl *tert*-butyl ether (1.7 kg). The solids were dried under vacuum at 50 °C to give 3.2 kg (68%) of **11**. ^{1}H NMR (DMSO-d_6) δ 2.45 (m, 1 H), 3.00 (m, 3 H), 3.15 (d, 3 H, J = 2.5), 3.43 (s, 2 H), 3.47(s, 3 H), 3.60 (m, 1 H), 4.87 (d, 1 H, J = 5.1), 5.47 (t, 1 H, J = 5.8), 6.27 (d, 1H, J = 14.4), 6.39 (s, 1 H), 7.02 (t, 1 H). Anal. Calcd for $C_{14}H_{18}FN_3O_4$: C, 54.01; H, 5.83; N, 13.50; F, 6.10. Found: C, 53.90; H, 5.62; N, 13.31; F, 6.16.

(*S*)-[3-(7-Fluoro-1-methyl-2-oxo-2,3-dihydro-1H-indol-5-yl)-2-oxo-oxazolidin-5-ylmethyl]carbamic Acid Methyl Ester (1). A glass-lined reactor was charged with **11** (3.2 kg, 10.3 mol) followed by CDI (2.1 kg, 13 mol) and acetonitrile (31 kg). The contents of the reactor were heated to 30 °C and stirred for 3 h at which point the reaction was complete. The contents were heated to 65 °C and held for 1 h followed by the addition of water (4.4 kg) and a hot filtration. The contents of the reactor were cooled to −5 °C and isolated by filtration. The resulting filter cake was recrystallized from acetonitrile (21.5 kg) and water (2.7 kg), cooled to −5 °C, and filtered. Upon drying at ambient temperature and vacuum filtering, 2.97 kg of **1** was isolated as an off-white solid (77%). ^{1}H NMR (DMSO-d_6) δ 3.22 (d, 3 H, J = 2.5), 3.22 (t, 2 H, J = 5.8), 3.52 (s, 3 H), 3.57 (s, 2 H), 3.70 (m, 1 H), 4.03 (m, 1 H), 4.64 (m, 1 H), 7.30 (s, 2 H), 7.52 (broad t, 1 H, J = 5.8);^{13}C NMR (DMSO-d_6) δ 174.40, 157.88, 154.74, 147.83, 145.45, 134.29, 134.20, 128.86, 128.81, 127.65, 127.57, 111.58, 106.25, 105.10, 72.08, 52.24, 48.09, 43.94, 40.71, 40.50, 36.38, 28.68, 28.63. Anal. Calcd for $C_{15}H_{16}FN_3O_5$: C, 53.41; H, 4.78; N, 12.46; F, 5.63. Found: C, 53.24; H, 4.43; N, 12.35; F, 5.53; MS m/z 338 (M^+).

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