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ANALOGS OF 4-(3-BROMO-8-METHYL-10-METHOXY-6,11-DIHYDRO-5H-BENZO[5,6]-CYCLOHEPTA[1,2-b]PYRIDIN-11-YL)-1-(4-PYRIDINYLACETYL)PIPERIDINE N-OXIDE AS INHIBITORS OF FARNESYL PROTEIN TRANSFERASE

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Abstract: A series of 3-substituted analogs **3** of 4-(3-bromo-8-methyl-10-methoxy-6,11-dihydro-5*H*-benzo[5,6]-cyclohepta[1,2*b*]pyridin-11-yl)-1-(4-pyridinylacetyl)piperidine N-oxide **2** was prepared and evaluated as FPT inhibitors. The objective of this study was to identify other substituents at C_3 in this series of FPT inhibitors that would have the FPT potency enhancement similar to that found for a C_3 bromo substituent. The 3-methyl analog **17b** was found to be tenfold less active than **2**, and other C_3 substituents having more steric bulk were found to cause a further reduction in activity. © 1999 Elsevier Science Ltd. All rights reserved.

Introduction

Ras proteins are GTP-binding proteins that play an important role in the signal transduction process in cell proliferation.¹ The proteins are expressed in the cytosol and acquire functionality by undergoing post-translational farnesylation of the cysteine residue in the C-terminus CaaX tetrapeptide catalyzed by the enzyme farnesyl protein transferase (FPT).² In normal cell growth, intrinsic GTPase activity of Ras allows its cycling between the active GTP-bound Ras and the inactive GDP-bound forms. Oncogenic Ras proteins, which are found in a large percentage of human cancers, are deficient in GTPase activity and hence are constitutively activated to promote uncontrolled cell division.³ Inhibition of FPT catalyzed farnesylation would potentially render oncogenic Ras non-functional and hence this concept has been the subject of intense interest as a therapeutic approach for the development of antitumor agents to treat *ras* associated tumors.⁴ Several structural types of potent FPT inhibitors have been reported in the literature during the past few years and this subject has been reviewed.⁵



Our laboratories have recently reported on the extensive structure-activity effort that culminated in the development of the trihalo benzocycloheptapyridine 1 (Sch 66336) as a highly potent (FPT inhibitor), orally active antitumor agent that is currently undergoing clinical trials in humans.⁶ The SAR studies leading to the development

of 1 showed that improvements in the potency and pharmacokinetics of the benzocycloheptapyridine FPT inhibitors were achievable by the introduction of a 3-bromo, a 7- bromo or a 10-bromo substituents, and a C_{11} -piperazine or piperidine pendant ring acylated by a 4-pyridylacetyl N-oxide or a 4-N-carboxamidopiperidinylacetyl group.⁶⁻⁹ As part of a study to explore novel inhibitor analogs of 1, we found that an 8-methyl and a 10-methoxy groups are effective equivalents of the 8,10-dihalo substituents resulting in the potent FPT inhibitor 2.¹⁰ Previous SAR studies of 3-substituted benzocycloheptapyridines established that only nonpolar, hydrophobic substituents with low steric bulk, such as a methyl group, elicited a potency enhancement of FPT inhibition activity similar to that observed for a 3-bromo substituent.^{7a} We report here the synthesis and FPT activity of several 3-alkyl substituted compounds 3. The objective of this study was to explore the FPT activity of C₃ alkyl analogs of 2. Chemistry

Compounds 3 were synthesised by applying the general methodology for the synthesis of the bencycloheptapiperidines.¹¹ For the synthesis of the 3-methyl tricyclic ketone 8 (Scheme 1), picoline $6^{11b,12}$ was alkylated with the 2-chloro benzyl bromide 5, obtained from a two step halogenation of 4, followed by treatment of the *t*-butylamide with phosphorous oxychloride to afford the desired cyclization precursor 7. The chlorine substituent in 7 was used as a blocking group for the directed triflic acid catalyzed electrophilic cyclization step to



Reagents: (a) i. N-Cl-succinimide/CH₃CN/70 °C ii. NBS /Benzoyl peroxide/CCl₄. (b) i. LDA/THF, -78 °C/5 ii. POCl₃/PhCH₃/80 °C. (c) i. CF₃SO₃H/rt ii. 2 N HCl/110 °C.

obtain 8, which was then reacted (Scheme 2) with N-Me-4-piperidinyl magnesium chloride to form the adduct **9b**. Ethylchloroformate mediated N-demethylation of **9b** followed by hydrogenolysis of the 7-chloro group, dehydration with PPA, acid hydrolysis of the N-ethylcarbamate and finally, reduction of the 11-ene with DIBAL afforded **10b**. DIBAL reduction of the 11-ene in **11**,¹⁰ afforded **10a** as a side-product. Protection of the NH in **11** as the N-Boc derivative followed by vinylation using Stille methodology¹³ afforded the 3-vinyl derivative **12** in high yield (94%). Cyclopropanation of the vinyl group of **12** with diazomethane-palladium acetate,¹⁴ TFA deprotection of the N-Boc, followed by reduction of the 11-ene with DIBAL afforded the 3-cyclopropyl derivative



Reagents: (a) N-Me-4-piperidinyl-MgCl. (b) i. ClCO₂Et/PhCH₃/70 °C ii. H₂/10%Pd-C/ MeOH iii. PPA/70 °C iii. 4 N HCl/110 °C iv. DIBALH/PhCH₃/rt. (c) i. (BOC)₂O/CH₂Cl₂ ii. Bu₃SnCH=CH₂/Pd(dba)₃/P(2-furyl)₃/LiCl/PhCH₃/100 °C/24 h. (d) i. CH₂N₂-Et₂O/ Pd(OAc)₂/CH₂Cl₂ ii. 20% TFA/CH₂Cl₂ iii. DIBALH/PhCH₃/rt. (e) i. (BOC)₂O/THF ii. BuLi-hexane/THF iii. Me₂CO. (f) i. 20% TFA/CH₂Cl₂ ii. DIBALH/PhCH₃/rt. (g) 10%Pd-C/HCO₂NH₄/MeOH/reflux. (h) EDCI/HOBT/NMM /4-pyridyl acetic acid N-oxide/DMF. (i) DIBALH/PhCH₃/rt.

13. TFA deprotection of the N-Boc of 12 followed by DIBAL reduction of the 11-ene afforded the 3-vinyl derivative 15; catalytic hydrogenation of 15 afforded the 3-ethyl derivative 16. Metalation of the 3-bromo of Boc-11 with BuLi, reaction with acetone followed by DIBAL reduction afforded the 3-isopropanol derivative 14. The NH precursors 10, 13–16 were acylated with 4-pyridyl acetic acid N-oxide in the presence of EDCI to afford the final compounds 17a–f.¹⁵

Biology

Compounds 17a-f were tested in the in vitro FPT assay which measures the inhibition of FPT-catalyzed transfer of ¹H-farnesyl group from ¹H-farnesylpyrophosphate to H-Ras-CVLS. Details of this test have been described previously.⁶ The FPT activity of the compounds in this enzymatic test is summarized in Table 1. Data in the Table show that the 3-unsubstituted compound **17a** is approximately 40x less active than the 3-bromo

reference compound 2. Introduction of a 3-methyl group as in **17b** improves the inhibitory activity fivefold. The 3-ethyl, and 3-vinyl compounds **17c** and **17d** are comparable in activity to the 3-methyl analog. Replacement of the 3-methyl group by cyclopropyl as in **17e** leads to a loss of activity equivalent to that of the 3-H compound **17a**. The 3-isopropanol derivative is only weakly active as a FPT inhibitor.

Entry No.	Substituents R	FPT ^a IC ₅₀ (µM)
17b	3-Methyl	0.034
17c	3-Ethyl	0.074
17d	3-Vinyl	0.059
17e	3-cycloPropyl	0.200
17f	3-C(OH)Me ₂	26% (0.19)
2	Bromo	0.0036

Conclusions

Previous SAR studies of 3-substituted 8-chloro-benzocycloheptapyridines have shown that the potency enhancement of FPT inhibition activity by a 3-methyl substituent is equivalent to that of a 3-bromo group and the compounds are 6x more active than the 3-H analog.^{7a} In the present series of 8-methyl-10-methoxybenzocycloheptapyridines, a 3-methyl substituent showed a similar improvement in activity but was found to be much less effective than a 3-bromo group. Furthermore, the 3-bromo group in this series elicits a much higher potency enhancement than in the reported^{7a} 8-chloro-benzocycloheptapyridines. Increasing the steric bulk of the 3-substituent leads to a loss in activity. None of the alkyl groups investigated here were found to be useful as replacements for the 3- bromo group.

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References

- (a) Egan, S. E.; Weinberg, R. A. Nature 1993, 365, 781; (b) Marshal, M. S. Trends Biochem. Sci. 1993, 18, 250; (c) Hall, A. Science 1994, 264, 1413.
- (a) Casey, P. J.; Solski, P. A.; Der, C. J.; Buss, J. E. Pro. Natl. Acad. Sci. U.S.A. 1989, 86, 8323. (b) Zhang, F. L.; Casey, P. J. Annu. Rev. Biochem. 1996, 65, 241.
- 3. For leading references describing the biology of *ras* see: (a) Barbacid, M. Annu. Rev. Biochem. 1987, 56, 779; (b) Bos, J. L. Cancer Res. 1989, 49, 4682.
- 4. Leonard, D. M. J. Med. Chem. 1997, 40, 2971.
- 5. Ayral-Kaloustian, S.; Skotnicki, J. S. Annu. Rep. Med. Chem. 1996, 31, 2971.
- Njoroge, G. F.; Taveras, A.G.; Kelly, J.; Remiszewski, S.; Mallams, A. K.; Wolin, R.; Afonso, A.; Cooper, A. B.; Rane, D. F.; Liu, Y.-T.; Wong, J.; Vibulbhan, B.; Pinto, P.; Deskus, J.; Alvarez, C. S.; del Rosario, J.; Connolly, M.; Wang, J.; Desai, J.; Rossman, R.; Bishop, W. R.; Patton, R.; Wang, L.; Kirshmeier, P.; Bryant, M.; Nomeir, A. A.; Lin, C.-C.; Liu, M.; McPhail, A. T.; Doll, R. J.; Girijavallabhan, V.; Ganguly, A. K. J. Med. Chem. 1998, 41, 4890

- (a) Njoroge, G. F.; Vibulbhan, B.; Rane, D. F.; Bishop, W. R.; Petrin, J.; Patton, R.; Bryant, M. S.; Chen, K.-J.; Nomeir, A. A.; Lin, C.-C.; Liu, M.; King, I.; Chen, J.; Lee, S.; Yaremko, B.; Dell, J.; Lipari, P.; Malkowski, M.; Li, Z.; Catino, J.; Doll, R. J.; Girijavallabhan, V.; Ganguly, A. K. J. Med. Chem. 1997, 40, 4290. (b) Njoroge, G. F.; Vibulbhan, B.; Pinto, P.; Chan, T.-M.; Osterman, R.; Remiszewski, S.; del Rosario, J.; Doll, R. J.; Girijavallabhan, V.; Ganguly, A. K. J. Org. Chem. 1998, 63, 445.
- Mallams, A. K.; Rossman, R.; Doll, R. J.; Girijavallabhan, V.; Ganguly, A. K.; Petrin, J.; Wang, L.; Patton, R.; Bishop, W. R.; Carr, D. M.; Kirshmeier, P.; Catino, J.; Bryant, M. S.; Chen, K.-J.; Korfmacher, W. A.; Nardo, C.; Wang, S.; Nomeir, A. A.; Lin, C.-C.; Li, Z.; Chen, J.; Lee, S.; Dell, J.; Lipari, P.; Malkowski, M.; Yaremko, B.; King, I.; Liu, M. J. Med. Chem. 1998, 41, 877.
- Njoroge, G. F.; Vibulbhan, B.; Pinto, P.; Bishop, W. R.; Bryant, M. S.; Nomeir, A. A.; Lin, C.-C.; Liu, M.; Doll, R. J.; Girijavallabhan, V.; Ganguly, A. K. J. Med. Chem. 1998, 41, 1561.
- Afonso, A.; Weinstein, J.; Kelly, J.; Wolin, R.; Rosenblum, S. B.; Connolly, M.; Guzi, T.; James, L.; Carr, D.; Patton, R.; Bishop, W. R.; Kirshmeier, P.; Liu, M.; Heimark, L.; Chen, K. J.; Nomeir, A. A. *Bioorg. Med. Chem.* 1999, 7, in press.
- (a) Schumacher, D. P.; Murphy, B. L.; Clark, J. E.; Tahbaz, P.; Mann, T. A. J. Org. Chem. 1989, 54, 2242. (b) Wong, J. K.; Piwinski, J. J.; Green, M. J.; Ganguly, A. K.; Anthes, J. C.; Billah, M. M. Bioorg. Med. Chem. Lett. 1993, 3, 1073. (c) Piwinski, J. J.; Wong, J. K.; Chan, T. K.; Green, M. J.; Ganguly, A. K. J. Org. Chem. 1990, 55, 3341. (d) Piwinski, J. J.; Wong, J. K.; Green, M. J. U.S. Patent 5, 422, 351 June 6, 1995; Chem. Abstr. 1992, 116, 235654. (e) Villani, F.J.; Daniels, P.J. L.; Ellis, C. A.; Mann, T. A.; Wang, K.-C. J. Heterocycl. Chem. 1971, 8, 73. (f) Villani, F.J.; Daniels, P.J. L.; Ellis, C. A.; Mann, T. A.; Wang, K.-C.; Wefer, E. A. J. Med. Chem. 1972, 15, 750.
- 12. Blank, B.; DiTullio, N. W.; Krog, A. J.; Saunders, H. L. J. Med. Chem. 1979, 22, 840.
- (a) Stille, J. K. Angew. Chem., Int. Ed. Engl. 1986, 25, 508. (b) Farina, V.; Krishnan, B. J. J. Am. Chem. Soc. 1991, 113, 9585.
- 14. Hildebrand, J. P.; Marsden, S. P. Synlett 1996, 893.
- 15. Physical data for compounds: 7: cryst. solid (66%): MS(CI) *m/z* 301 (MH⁺).8: cryst solid (76%): mp 188–190 °C; MS(CI) *m/z* 302, 304 (MH⁺). 9b: white powder (76%): ¹H NMR (300 MHz, CDCl₃) δ 2.29 (s, 3H), 2.34 (s, 3H), 2.79 (s,3H), 3.89 (s, 3H), 6.83 (s, 1H), 7.67 (s, 1H), 8.22 (s, 1H); HRMS (FAB) calcd for C₂₃H₃₀N₂O₂Cl 401.1996, found 401.2001. 10b: off-white powder (27%): ¹H NMR (300 MHz, CDCl₃) δ 2.23 (s, 3H), 2.28 (s, 3H), 3. 76 (s, 3H), 4.83 (d, 1H, *J* = 10.4 Hz), 6.65 (s, 1H), 6.57, (s, 1H), 7.17 (s, 1H), 8.17 (s, 1H); MS(CI) *m/z* 337 (MH⁺). 12: ¹H NMR (300 MHz, CDCl₃) δ 1.45 (s,9 H), 2.15 (m, 1H), 2.25 (m, 1H), 2.31 (s, 3H), 2.37 (m, 1H), 2.57 (m, 1H), 2.70 (m, 1H), 2.90 (m,1 H), 3.0-3.2 (m, 2H), 3.2-3.5 (m, 2H), 3.75 (s, 3H), 5.28 (d, 1H, *J* = 10.9 Hz), 5.73 (d, 1H, *J* = 17.5 Hz), 6.57 (s, 1H), 6.62 (m, 1H), 6.66 (s, 1H), 7.38 (s, 1H), 8.41 (s,1H); MS(CI) *m/z* 445 (MH⁺). 13: ¹H NMR (300 MHz, CDCl₃) δ 0.64 (d, 2H, *J* = 4 Hz), 0.93 (d, 2H, *J* = 8.4 Hz), 2.28 (s, 3H), 3.76 (s, 3H), 4.82 (d, 1H, *J* = 10.5 Hz), 6.55, (s, 1H), 6.56 (s, 1H), 6.96 (s, 1H), 8.14 (d, 1H, *J* = 2 Hz); HRMS (FAB) calcd for C₂₄H₃₁N₂O

363.2436, found 363.2441. 14: ¹H NMR (300 MHz, CDCl₃) & 1.54, 1.56 (s, 6H), 2.28 (s, 3H), 3.71 (s, 3H), 4.85 (d, 1H, J = 10.5 Hz), 6.55, (s, 1H), 6.58 (s, 1H), 7.48 (d, 1H, J = 2 Hz), 8.13 (d, 1H, J = 6.8Hz), 8.43 (d, 1H, J = 2 Hz); HRMS (FAB) calcd for $C_{24}H_{33}N_2O_2$ 381.2542, found 381.2544. 15: ¹H NMR $(300 \text{ MHz}, \text{CDCl}_3) \delta 1.39 \text{ (m, 4H)}, 2.25 \text{ (m, 1H)}, 2.28 \text{ (s, 3H)}, 2.45 \text{ (m, 2H)}, 2.8-3.1 \text{ (m, 4H)}, 3.37 \text{ (m, 2H)}, 2.8-3.1 \text{ (m, 4H)}, 3.37 \text{ (m, 2H)}, 3.37 \text{ (m, 2$ 1H), 3.57 (m, 1H), 3.77 (s, 3H), 4.86 (d, 1H, J = 10.5Hz), 5.28 (d, 1H, J = 10.5 Hz), 5.74 (d, 1H, J = 10.5Hz), 5.74 (d, 1H, J = 10.5Hz 17.7 Hz), 6.56 (s, 1H), 6.58 (s, 1H), 6.63 (m, 1H), 7.41 (s, 1H), 8.35 (s, 1H); HRMS (FAB) calcd for $C_{23}H_{28}N_2O$ 349.2280, found 349.2280. 16: ¹H NMR (300 MHz, CDCl₃) δ 1.18 (t, 3H, J = 7.4 Hz), 1.7 (m, 5H), 2.28 (s, 3H), 2.55 (q, 2H, J = 7.6Hz), 2.73 (m, 4H), 3.2-3.5 (m, 4H), 3.69 (s, 3H), 4.83 (d, 1H, J = 7.6Hz), 2.73 (m, 4H), 3.2-3.5 (m, 4H), 3.69 (s, 3H), 4.83 (d, 1H, J = 7.6Hz), 2.73 (m, 4H), 3.2-3.5 (m, 4H), 3.69 (s, 3H), 4.83 (d, 1H, J = 7.6Hz), 2.73 (m, 4H), 3.2-3.5 (m, 4H), 3.69 (s, 3H), 4.83 (d, 1H, J = 7.6Hz), 2.73 (m, 4H), 3.2-3.5 (m, 4H), 3.69 (s, 3H), 4.83 (d, 1H, J = 7.6Hz), 2.73 (m, 4H), 3.2-3.5 (m, 4H), 3.69 (s, 3H), 4.83 (d, 1H, J = 7.6Hz), 2.73 (m, 4H), 3.2-3.5 (m, 4H), 3.69 (s, 3H), 4.83 (d, 1H, J = 7.6Hz), 2.73 (m, 4H), 3.2-3.5 (m, 4H), 3.69 (s, 3H), 4.83 (d, 1H, J = 7.6Hz), 2.73 (m, 4H), 3.2-3.5 (m, 4H), 3.69 (s, 3H), 4.83 (d, 1H, J = 7.6Hz), 2.73 (m, 4H), 3.2-3.5 (m, 4H), 3.69 (s, 3H), 4.83 (d, 1H, J = 7.6Hz), 2.73 (m, 4H), 3.2-3.5 (m, 4H), 3.69 (s, 3H), 4.83 (d, 1H, J = 7.6Hz), 2.73 (m, 4H), 3.2-3.5 (m, 4H), 3.69 (s, 3H), 4.83 (d, 1H, J = 7.6Hz), 2.73 (m, 4H), 3.2-3.5 (m, 4H), 3.69 (s, 3H), 4.83 (d, 1H, J = 7.6Hz), 2.73 (m, 4H), 3.2-3.5 (m, 4H), 3.69 (s, 3H), 4.83 (d, 1H, J = 7.6Hz), 2.73 (m, 4H), 3.2-3.5 (m, 4H), 3.69 (s, 3H), 4.83 (d, 1H, J = 7.6Hz), 2.74 (m, 2H), 2.75 (m, 2H), 2.75 (m, 2H), 3.6Hz), 3.75 (m, 2H), 3.75 (m, 2H), 3.6Hz), 3.75 (m, 2H), 3.75 (m, 2H), 3.6Hz), 3.75 (m, 2H), 10.2 Hz), 6.52 (s, 1H), 6.55 (s, 1H), 7.16 (s, 1H), 8.09 (s, 1H); MS(ES) m/z 351 (MH⁺). 17a: ¹H NMR (300 MHz, CDCl₃) δ 2.30 (s, 3H), 2.54 (m, 2H), 2.89 (m, 4H), 3.32 (m, 2H), 3.65 (s, 2H), 3.78 (s, 3H), 4.50 (m, 1H), 4.97 (m, 1H), 6.57 (s, 1H), 6.59 (s, 1H), 7.09 (m, 1H), 7.14 (s, 1H), 7.16 (s, 1H), 7.39 (d, 1H, J = 7.3 Hz), 8.15 (s, 1H), 8.17 (s, 1H), 8.35 (d, 1H J = 3.7 Hz); HRMS (FAB) calcd for $C_{28}H_{32}N_3O_3$ 458.2444, found 458.2436. 17b: ¹H NMR (300 MHz, CDCl₃) δ 2.24 (s, 3H), 2.29 (s, 3H), 3.64 (s, 2H), 3.76 (s, 3H), 6.56 (s, 1H), 6.59 (s, 1H), 7.14 (d, 2H, J = 6.8 Hz), 7.20 (s, 1H), 8.14 (d, 2H J = 6.8 Hz), 8.18 (s, 1H); HRMS (FAB) calcd for C₂₉H₃₃N₃O₃ 472.2600 found 472.2605. **17c**: ¹H NMR $(400 \text{ MHz,CDCl}_3) \delta 1.20 \text{ (t, 3H, } J = 7.48 \text{ Hz}), 1.47 \text{ (m, 4H)}, 2.29 \text{ (s, 3H)}, 2.35 \text{ (m, 1H)}, 2.53 \text{ (m, 1H)}, 2.53$ 2.55 (q, 2H), 2.85 (m, 1H), 2.92 (m, 2H), 3.28 (m, 1H), 3.48 (m, 1H), 3.64 (s, 2H), 3.74 (m, 1H), 3.77 (s, 3H) 4.50 (m, 1H), 4.83 (m, 1H), 6.56 (s, 1H), 6.59 (s, 1H), 7.14 (d, 2H, J = 6.16 Hz), 7.19 (s, 1H), 8.14 (d, 2H, J = 5.24 Hz), 8.18 (s, 1H); HRMS (FAB) calcd for $C_{30}H_{36}N_3O_3$ 486.2757, found 486.2755. **17d**: ¹H NMR (300 MHz, CDCl₃) δ 1.47 (m, 4H), 2.29 (s, 3H), 2.35 (m, 1H), 2.52 (m, 1H), 2.86 (m, 1H), 2.88 3H), 3.35 (m, 1H), 3.55 (m, 1H), 3.64 (s, 2H), 3.74 (m, 1H), 3.77 (s, 3H), 4.50 (m, 1H), 4.87 (m, 1H), 5.32 (d, 1H, J = 11.2 Hz), 5.76 (d, 1H, J = 17.7 Hz), 6.57 (s, 1H), 6.59 (s, 1H), 6.64 (m, 1H), 7.14 (d, 2H, J = 6.57 Hz), 7.42 (s, 1H), 8.14 (d, 2H, J = 6.72 Hz), 8.35 (s, 1H); HRMS (FAB) calcd for $C_{30}H_{34}N_3O_3$ 484.2600, found 484.2601. 17e: ¹H NMR (300 MHz, CDCl₃) δ 0.65 (d, 2H, J = 4 Hz), 0.96 (d, 2H, J = 8 Hz), 2.28 (s, 3H), 3.64 (s, 2H), 3.75 (s, 3H), 4.80, 4.81 (d, 1H, J = 10.2 Hz), 6.55, (s, 1H),6.58 (s, 1H), 6.96 (s, 1H), 7.14 (d, 2H, J = 6.2 Hz), 8.12 (bs, 3H, J = 2 Hz); HRMS (FAB) calcd for $C_{31}H_{36}N_3O_3$ 498.2757, found 498.2752. **17f**: ¹H NMR (300 MHz, CDCl₃) δ 1.55, 1.56 (s, 6H), 2.29 (s, 3H), 3.63 (s, 2H), 3.75 (s, 3H), 4.50 (bt, 1H), 4.86, 4.85 (d, 1H, J = 10.3 Hz), 6.56, (s, 1H), 6.59 (s, 1H), 7.13 (d, 1H, J = 6.8 Hz), 7.50 (s, 1H), 8.13 (d, 1H, J = 6.8 Hz), 8.44 (s, 1H); HRMS (FAB) calcd for C₃₁H₃₈N₃O₄ 516.2862, found 516.2862.