Base mediated 1,6- Aza-Michael addition of heterocyclic amines and amides to p-QMs leading to Meclizine, Hydroxyzine and Cetirizine like architectures

Deblina Roy and Gautam Panda*
Lab No. CSS 106, Medicinal and Process Chemistry Division, CSIR-Central Drug Research Institute, Sitapur Road, Jankipuram Extension, Lucknow-226031, UP, India

Contents:

<table>
<thead>
<tr>
<th>Description</th>
<th>Page No</th>
</tr>
</thead>
<tbody>
<tr>
<td>$^1$H, $^{13}$C NMR spectra of compounds (3a-3z’)</td>
<td>2-55</td>
</tr>
<tr>
<td>$^1$H, $^{13}$C NMR spectra of compounds (7-8)</td>
<td>56-59</td>
</tr>
<tr>
<td>HRMS of compounds 3b, 3c, 3d, 3f, 3g, 3h, 3i, 3m, 3n, 3o, 3r, 3s, 3w, 3z, 3z’, 8</td>
<td>60-75</td>
</tr>
<tr>
<td>HPLC spectra of 3k (both powder and crystal form)</td>
<td>76-77</td>
</tr>
<tr>
<td>Mono detertbutylated Product</td>
<td>78</td>
</tr>
</tbody>
</table>
Figure S-1. $^1$H NMR spectrum of 2,6-di-tert-butyl-4-((4-methylpiperazin-1-yl)(phenyl)methyl)phenol (3a)
Figure S-2. $^{13}$C NMR spectrum of 2,6-di-tert-butyl-4-((4-methylpiperazin-1-yl)(phenyl)methyl)phenol (3a)
Figure S-3. $^1$H NMR spectrum of 4-((2-bromophenyl)(thiomorpholino)methyl)-2,6-di-tert-butylphenol (3b)
Figure S-4. $^{13}$C NMR spectrum of 4-((2-bromophenyl)(thiomorpholino)methyl)-2,6-di-tert-butylphenol (3b)
Figure S-5. $^1$H NMR spectrum of 4-((2-bromophenyl)(4-methylpiperazin-1-yl)methyl)-2,6-di-tert-butylphenol (3c)
Figure S-6. $^{13}$C NMR spectrum of 4-((2-bromophenyl)(4-methylpiperazin-1-yl)methyl)-2,6-di-tert-butylphenol (3c)
Figure S-7. $^1$H NMR spectrum of 1-((2-bromophenyl)(3,5-di-tert-butyl-4-hydroxyphenyl)methyl)pyrrolidin-2-one (3d)
Figure S-8. $^{13}$C NMR spectrum of 1-((2-bromophenyl)(3,5-di-tert-butyl-4-hydroxyphenyl)methyl)pyrrolidin-2-one (3d)
Figure S-9. $^1$H NMR spectrum of 4-((2-bromophenyl)(1H-1,2,4-triazol-1-yl)methyl)-2,6-di-tert-butylphenol (3e)
Figure S-10. $^{13}$C NMR spectrum of 4-((2-bromophenyl)(1H-1,2,4-triazol-1-yl)methyl)-2,6-di-tert-butylphenol (3e)
Figure S-11. $^1$H NMR spectrum of 4-((4-benzylpiperazin-1-yl)(2-bromophenyl)methyl)-2,6-di-tert-butylphenol (3f)
Figure S-12. $^{13}$C NMR spectrum of 4-((4-benzylpiperazin-1-yl)(2-bromophenyl)methyl)-2,6-di-tert-butylphenol (3f)
Figure S-13. $^1$H NMR spectrum of 4-((2-bromophenyl)(morpholino)methyl)-2,6-di-tert-butylphenol (3g)
Figure S-14. $^{13}$C NMR spectrum of 4-((2-bromophenyl)(morpholino)methyl)-2,6-di-tert-butylphenol (3g)
Figure S-15. \( ^1H \) NMR spectrum of 4-((2-bromophenyl)(1H-imidazol-1-yl)methyl)-2,6-di-tert-butylphenol (3h)
Figure S-16. $^{13}$C NMR spectrum of 4-((2-bromophenyl)(1H-imidazol-1-yl)methyl)-2,6-di-tert-butylphenol (3h)
Figure S-17. $^1$H NMR spectrum of 4-((2-bromophenyl)(piperidin-1-yl)methyl)-2,6-di-tert-butylphenol (3i)
Figure S-18. $^{13}$C NMR spectrum of 4-((2-bromophenyl)(piperidin-1-yl)methyl)-2,6-di-tert-butylphenol (3i)
Figure S-19. $^1$H NMR spectrum of 2,6-di-tert-butyl-4-((4-chlorophenyl)(morpholino)methyl)phenol (3j)
Figure S-20. $^{13}$C NMR spectrum of 2,6-di-tert-butyl-4-((4-chlorophenyl)(morpholino)methyl)phenol (3j)
Figure S-21. $^1$H NMR spectrum of 2,6-di-tert-butyl-4-((4-chlorophenyl)(4-methylpiperazin-1-yl)methyl)phenol (3k)
Figure S-22. $^{13}$C NMR spectrum of 2,6-di-tert-butyl-4-((4-chlorophenyl)(4-methylpiperazin-1-yl)methyl)phenol (3k)
Figure S-23. $^1$H NMR spectrum of 2,6-di-tert-butyl-4-((4-chlorophenyl)(4-(2-fluorophenyl)piperazin-1-yl)methyl)phenol (3l)
Figure S-24. $^{13}$C NMR spectrum of 2,6-di-tert-butyl-4-((4-chlorophenyl)(4-(2-fluorophenyl)piperazin-1-yl)methyl)phenol (3l)
Figure S-25. $^1$H NMR spectrum of 2,6-di-tert-butyl-4-((4-chlorophenyl)(thiomorpholino)methyl)phenol (3m)
Figure S-26. $^{13}\text{C}$ NMR spectrum of 2,6-di-tert-butyl-4-((4-chlorophenyl)(thiomorpholino)methyl)phenol (3m)
Figure S-27. $^1$H NMR spectrum of 1-((4-chlorophenyl)(3,5-di-tert-butyl-4-hydroxyphenyl)methyl)pyrrolidin-2-one (3n)
Figure S-28. $^{13}$C NMR spectrum of 1-((4-chlorophenyl)(3,5-di-tert-butyl-4-hydroxyphenyl)methyl)pyrrolidin-2-one (3n)
Figure S-29. $^1$H NMR spectrum of 4-((4-benzylpiperazin-1-yl)(4-chlorophenyl)methyl)-2,6-di-tert-butylphenol (3o)
Figure S-30. $^{13}$C NMR spectrum of 4-((4-benzylpiperazin-1-yl)(4-chlorophenyl)methyl)-2,6-di-tert-butylphenol (3o)
Figure S-31. $^1$H NMR spectrum of 2,6-di-tert-butyl-4-((4-chlorophenyl)(1H-1,2,4-triazol-1-yl)methyl)phenol (3p)
Figure S-32. $^{13}$C NMR spectrum of 2,6-di-tert-butyl-4-((4-chlorophenyl)(1H-1,2,4-triazol-1-yl)methyl)phenol (3p)
Figure S-33. $^1$H NMR spectrum of 3-((4-chlorophenyl)(3,5-di-tert-butyl-4-hydroxyphenyl)methyl)oxazolidin-2-one (3q)
Figure S-34. $^{13}$C NMR spectrum of 3-((4-chlorophenyl)(3,5-di-tert-butyl-4-hydroxyphenyl)methyl)oxazolidin-2-one (3q)
Figure S-35. $^1$H NMR spectrum of 2,6-di-tert-butyl-4-((4-chlorophenyl)(4-(3-methylbenzyl)piperazin-1-yl)methyl)phenol (3r)
Figure S-36. $^{13}$C NMR spectrum of 2,6-di-tert-butyl-4-((4-chlorophenyl)(4-(3-methylbenzyl)piperazin-1-yl)methyl)phenol (3r)
Figure S-37. $^1$H NMR spectrum of 1-((3,5-di-tert-butyl-4-hydroxyphenyl)(3,4,5-trimethoxyphenyl)methyl)pyrrolidin-2-one (3s)
Figure S-38. $^{13}$C NMR spectrum of 1-((3,5-di-tert-butyl-4-hydroxyphenyl)(3,4,5-trimethoxyphenyl)methyl)pyrrolidin-2-one (3s)
Figure S-39. $^1$H NMR spectrum of 4-((1H-imidazol-1-yl)(4-methoxyphenyl)methyl)-2,6-di-tert-butylphenol (3t)
Figure S-40. $^{13}$C NMR spectrum of 4-((1H-imidazol-1-yl)(4-methoxyphenyl)methyl)-2,6-di-tert-butylphenol (3t)
Figure S-41. $^1$H NMR spectrum of 2,6-di-tert-butyl-4-(morpholino(3,4,5-trimethoxyphenyl)methyl)phenol (3u)
Figure S-42. $^{13}$C NMR spectrum of 2,6-di-tert-butyl-4-(morpholino(3,4,5-trimethoxyphenyl)methyl)phenol (3u)
Figure S-43. $^1$H NMR spectrum of 4-([1,1'-biphenyl]-4-yl(morpholino)methyl)-2,6-di-tert-butylphenol (3v)
Figure S-44. $^{13}$C NMR spectrum of 4-([1,1'-biphenyl]-4-yl(morpholino)methyl)-2,6-di-tert-butylphenol (3v)
Figure S-45. $^1$H NMR spectrum of 4-((6-bromo-2-methoxyquinolin-3-yl)(piperidin-1-yl)methyl)-2,6-di-tert-butylphenol (3w)
Figure S-46. $^{13}$C NMR spectrum of 4-((6-bromo-2-methoxyquinolin-3-yl)(piperidin-1-yl)methyl)-2,6-di-tert-butylphenol (3w)
Figure S-47. $^1$H NMR spectrum of 4-((4-benzylpiperazin-1-yl)(6-bromo-2-chloroquinolin-3-yl)methyl)-2,6-di-tert-butylphenol (3x)
Figure S-48. $^{13}$C NMR spectrum of 4-((4-benzylpiperazin-1-yl)(6-bromo-2-chloroquinolin-3-yl)methyl)-2,6-di-tert-butylphenol (3x)
Figure S-49. $^1$H NMR spectrum of 2,6-diisopropyl-4-((4-methylpiperazin-1-yl)(phenyl)methyl)phenol (3y)
Figure S-50. $^{13}$C NMR spectrum of 2,6-diisopropyl-4-((4-methylpiperazin-1-yl)(phenyl)methyl)phenol (3y)
Figure S-51. $^1$H NMR spectrum of 2,6-di-tert-butyl-4-((4-methylpiperazin-1-yl)(4-(trifluoromethoxy)phenyl)methyl)phenol (3z)
Figure S-52. $^{13}$C NMR spectrum of 2,6-di-tert-butyl-4-((4-methylpiperazin-1-yl)(4-(trifluoromethoxy)phenyl)methyl)phenol (3z)
Figure S-53. $^1$H NMR spectrum of 2,6-di-tert-butyl-4-((4-methylpiperazin-1-yl)(4-(trifluoromethyl)phenyl)methyl)phenol (3z')
Figure S-54. $^{13}$C NMR spectrum of 2,6-di-tert-butyl-4-((4-methylpiperazin-1-yl)(4-(trifluoromethyl)phenyl)methyl)phenol (3z')
Figure S-55. $^1$H NMR spectrum of 2-(2-(piperazin-1-yl)ethoxy)ethan-1-ol (7)
Figure S-56. $^{13}$C NMR spectrum of 2-(2-(piperazin-1-yl)ethoxy)ethan-1-ol (7)
Figure S-57. $^1$H NMR spectrum of 2,6-di-tert-butyl-4-((4-chlorophenyl)(4-(2-(2-hydroxyethoxy)ethyl)piperazin-1-yl)methyl)phenol (8)
Figure S-58. $^{13}$C NMR spectrum of 2,6-di-tert-butyl-4-((4-chlorophenyl)(4-(2-(2-hydroxyethoxy)ethyl)piperazin-1-yl)methyl)phenol (8)
Figure S-59. HRMS spectrum of 4-((2-bromophenyl)(thiomorpholino)methyl)-2,6-di-tert-butylphenol (3b)
Figure S-60. HRMS spectrum of 4-((2-bromophenyl)(4-methylpiperazin-1-yl)methyl)-2,6-di-tert-butylphenol (3c)
Figure S-61. HRMS spectrum of 1-((2-bromophenyl)(3,5-di-tert-butyl-4-hydroxyphenyl)methyl)pyrrolidin-2-one (3d)
Figure S-62. HRMS spectrum of 4-((4-benzylpiperazin-1-yl)(2-bromophenyl)methyl)-2,6-di-tert-butylphenol (3f)
Figure S-63. HRMS spectrum of 4-((2-bromophenyl)(morpholino)methyl)-2,6-di-tert-butylphenol (3g)
Figure S-64. HRMS spectrum of 4-((2-bromophenyl)(1H-imidazol-1-yl)methyl)-2,6-di-tert-butylphenol (3h)
Figure S-65. HRMS spectrum of 4-((2-bromophenyl)(piperidin-1-yl)methyl)-2,6-di-tert-butylphenol (3i)
Figure S-66. HRMS spectrum of 2,6-di-tert-butyl-4-((4-chlorophenyl)(thiomorpholino)methyl)phenol (3m)
Figure S-67. HRMS spectrum of 1-((4-chlorophenyl)(3,5-di-tert-butyl-4-hydroxyphenyl)methyl)pyrrolidin-2-one (3n)
Figure S-68. HRMS spectrum of 4-((4-benzylpiperazin-1-yl)(4-chlorophenyl)methyl)-2,6-di-tert-butylphenol (3o)
Figure S-69. HRMS spectrum of 2,6-di-tert-butyl-4-((4-chlorophenyl)(4-(3-methylbenzyl)piperazin-1-yl)methyl)phenol (3r)
Figure S-70. HRMS spectrum of 1-((3,5-di-tert-butyl-4-hydroxyphenyl)(3,4,5-trimethoxyphenyl)methyl)pyrrolidin-2-one (3s)
Figure S-71. HRMS spectrum of 4-((6-bromo-2-methoxyquinolin-3-yl)(piperidin-1-yl)methyl)-2,6-di-tert-butylphenol (3w)
Figure S-72. HRMS spectrum of 2,6-di-tert-butyl-4-((4-methylpiperazin-1-yl)(4-(trifluoromethoxy)phenyl)methyl)phenol (3z)
Figure S-73. HRMS spectrum of 2,6-di-tert-butyl-4-((4-methylpiperazin-1-yl)(4-(trifluoromethyl)phenyl)methyl)phenol (3z’)
Figure S-74. HRMS spectrum of 2,6-di-tert-butyl-4-((4-chlorophenyl)(4-(2-(2-hydroxyethoxy)ethyl)piperazin-1-yl)methyl)phenol (8)
The enantiomeric excess was determined by HPLC with a Daicel Chiralpak IA column (n-hexane/Isopropanol/Diethylamine = 95/5/0.1, $\lambda = 254$ nm, 1 mL/min). For one isomer: $t_R = 3.94$ min, for another isomer: $t_R = 4.75$ min.

Figure S-75. HPLC spectrum of 2,6-di-tert-butyl-4-((4-chlorophenyl)(4-methylpiperazin-1-yl)methyl)phenol (3k)
The enantiomeric excess was determined by HPLC with a Daicel Chiralpak IA column (n-hexane/Isopropanol/Diethylamine = 95/5/0.1, $\lambda = 254$ nm, 1 mL/min). For one isomer: $t_R = 3.94$ min, for another isomer: $t_R = 4.78$ min. 0% ee.

**Figure S-76. HPLC spectrum of 2,6-di-tert-butyl-4-((4-chlorophenyl)(4-methylpiperazin-1-yl)methyl)phenol (3k)**
Figure S-77. $^1$H NMR spectrum of 1-((3-(tert-butyl)-4-hydroxyphenyl)(4-chlorophenyl)methyl)pyrrolidin-2-one (3n')