GREEN SYNTHESIS OF NOVEL PHTHALIMIDE DERIVATIVES
OF P-AMINOSALICYLIC ACID AS POTENTIAL ANTI-
TUBERCULOSIS AGENTS


Keywords: phthalic anhydrides; p-aminosalicylic acid; anti-tuberculosis agents; 4-(2-carboxybenzamido)-2-hydroxybenzoic acids; 4-(1,3-dioxoisindolin-2-yl)-2-hydroxybenzoic acids

Green synthesis of novel compounds 4-(2-carboxybenzamido)-2-hydroxybenzoic acids 3a-3e and 4-(1,3-dioxoisindolin-2-yl)-2-hydroxybenzoic acids 4a-4e have been developed in good yields which were analogues of p-aminosalicylic acid (used as anti-tuberculosis agent).

Introduction

Tuberculosis (TB), an infection of Mycobacterium tuberculosis, still remains the leading cause of worldwide deaths among infectious diseases. One-third of the population is infected with Mycobacterium tuberculosis and the World Health Organization (WHO) estimates that within the next 20 years about 30 million people will be infected with the bacillus. Considering TB problems, the WHO declared this disease a global health emergency in 1993. It is commonly known that Mycobacterium tuberculosis has developed resistance to the majority of the existing drugs. However, powerful new anti-TB drugs with new mechanisms of action have not been developed in the last forty years. Therefore, there is an urgent demand for a new class of anti-tubercular agent with a different mode of action and it has led medicinal chemists to explore a wide variety of chemical structures. p-Aminosalicylic acid (PAS) and its sodium salt are the drugs used to treat tuberculosis. Brand names are Tubasal, Nemasol sodium, etc. However, its potency is less than that of the current five first-line drugs (isoniazid, rifampicin, ethambutol, pyrazinamide, and streptomycin) for treating tuberculosis but it is still useful in the treatment of multidrug-resistant tuberculosis. PAS can cause some side effects including nausea, vomiting, abdominal pain, hepatitis and jaundice. So a promising approach to minimize these side effects is still in so much interest via analogues formation. On the other hand, phthalimide derivatives have been widely reported to possess beneficial pharmaceutical effects, like analgesic, anti-inflammatory and antiviral, etc.

Keeping the above details/facts in mind and in continuation of our earlier studies, on preparation of new derivatives of phthalic anhydride, it was considered worthwhile to prepare phthalimide derivatives of aspirin and p-aminosalicylic acid as potentially biologically active compounds and as new chemical entities.

Experimental section

A mixture of 1a-1e (10 mM), 2 (10 mM) and glycerol (20 ml) was heated at 40 °C for 10 min. At the end of this period, colourless solid separated out from reaction mixture which was collected by filtration, washed with hexane (10 ml) and dried. The crude product was recrystallized from a suitable solvent to obtain pure 3a-3e.

3a: Yield = 2.58 g (85%), M.P: 220–222 °C; IR (KBr) : 3038-3353 cm⁻¹ (broad, medium, -NH- and -OH groups put together), 1703 cm⁻¹ (sharp, strong, -CO- of acid group), 1690 cm⁻¹ (sharp, strong, -CO- of acid group), 1632 cm⁻¹ (sharp, strong, -CO- of amide group); ¹H-NMR (DMSO-d₆, 400 MHz) : δ 7.0 (s, 1H, -NH, D₂O exchangeable), 7.4-8.0 (m, 7H, Ar-H), 10.6 (s, 1H, -OH, D₂O exchangeable), 11.5 (s, 1H, -COOH, D₂O exchangeable) 13.2 (s, 1H, -COOH, D₂O exchangeable); ¹³C-NMR (DMSO-d₆, 400 MHz): δ
111.5, 112.3, 113.6, 116.7, 116.9, 122.7, 124.8, 127.6, 131.6, 133.3, 135.1, 140.2, 158.8, 172.6, 176.5; HRMS calcd for C_{15}H_{19}NO_{2} [M+H]^+: 302.5215. Found: 302.5212.

3b: Yield = 3.71 g (85%), M.P: >220 °C; IR (KBr): 3050-3350 cm\(^{-1}\) (broad, medium, -NH and -OH groups put together), 1705 cm\(^{-1}\) (sharp, strong, -CO of acid group), 1695 cm\(^{-1}\) (sharp, strong, -CO of acid group), 1630 cm\(^{-1}\) (sharp, strong, -CO of amide group) \(^1\)H-NMR (DMSO-d\(_6\), 400 MHz): \(\delta\) 7.2 (s, 1H, -NH, D\(_2\)O exchangeable), 7.4-8.0 (m, 3H, Ar-H), 10.4 (s, 1H, -OH, D\(_2\)O exchangeable), 11.6 (s, 1H, -COOH, D\(_2\)O exchangeable) 13.4 (s, 1H, -COOH, D\(_2\)O exchangeable); \(^1\)C-NMR (DMSO-d\(_6\), 400 MHz): \(\delta\) 111.3, 111.9, 112.6, 114.3, 115.8, 120.2, 123.4, 126.6, 130.6, 131.4, 134.2, 141.3, 157.0, 171.0, 176.0; HRMS calcd for C_{15}H_{19}ClNO_{2} [M+H]^+: 437.3232. Found: 437.3236.

3c: Yield = 5.12 g (83%), M.P: >220 °C; IR (KBr): 3050-3350 cm\(^{-1}\) (broad, medium, -NH and -OH groups put together), 1710 cm\(^{-1}\) (sharp, strong, -CO of acid group), 1690 cm\(^{-1}\) (sharp, strong, -CO of acid group), 1640 cm\(^{-1}\) (sharp, strong, -CO of amide group) \(^1\)H-NMR (DMSO-d\(_6\), 400 MHz): \(\delta\) 7.2 (s, 1H, -NH, D\(_2\)O exchangeable), 7.4-8.0 (m, 7H, Ar-H), 10.4 (s, 1H, -OH, D\(_2\)O exchangeable), 11.5 (s, 1H, -COOH, D\(_2\)O exchangeable) 13.2 (s, 1H, -COOH, D\(_2\)O exchangeable); \(^1\)C-NMR (DMSO-d\(_6\), 400 MHz): \(\delta\) 111.3, 111.9, 112.8, 114.4, 115.0, 117.7, 120.4, 123.4, 124.7, 126.3, 128.6, 132.7, 157.7, 171.0, 175.9; HRMS calcd for C_{15}H_{18}BrNO_{2} [M+H]^+: 617.7313. Found: 617.7317.

3d: Yield = 2.77 g (80%), M.P: >220 °C; IR (KBr): 3050-3350 cm\(^{-1}\) (broad, medium, -NH and -OH groups put together), 1705 cm\(^{-1}\) (sharp, strong, -CO of acid group), 1695 cm\(^{-1}\) (sharp, strong, -CO of acid group), 1625 cm\(^{-1}\) (sharp, strong, -CO of amide group) \(^1\)H-NMR (DMSO-d\(_6\), 400 MHz): \(\delta\) 7.4 (s, 1H, -NH, D\(_2\)O exchangeable), 7.4-8.0 (m, 6H, Ar-H), 10.4 (s, 1H, -OH, D\(_2\)O exchangeable), 11.7 (s, 1H, -COOH, D\(_2\)O exchangeable) 13.4 (s, 1H, -COOH, D\(_2\)O exchangeable); \(^1\)C-NMR (DMSO-d\(_6\), 400 MHz): \(\delta\) 110.3, 111.2, 113.4, 115.6, 115.9, 120.2, 124.5, 126.9, 130.3, 132.3, 134.1, 141.1, 157.8, 173.4, 176.8; HRMS calcd for C_{15}H_{19}NO_{2} [M+H]^+: 347.1216. Found: 347.1213.

3e: Yield = 2.77 g (80%), M.P: >220 °C; IR (KBr): 3050-3350 cm\(^{-1}\) (broad, medium, -NH and -OH groups put together), 1700 cm\(^{-1}\) (sharp, strong, -CO of acid group), 1690 cm\(^{-1}\) (sharp, strong, -CO of acid group), 1630 cm\(^{-1}\) (sharp, strong, -CO of amide group) \(^1\)H-NMR (DMSO-d\(_6\), 400 MHz): \(\delta\) 7.4 (s, 1H, -NH, D\(_2\)O exchangeable), 7.4-8.0 (m, 6H, Ar-H), 10.5 (s, 1H, -OH, D\(_2\)O exchangeable), 11.6 (s, 1H, -COOH, D\(_2\)O exchangeable) 13.6 (s, 1H, -COOH, D\(_2\)O exchangeable); \(^1\)C-NMR (DMSO-d\(_6\), 400 MHz): \(\delta\) 112.2, 113.8, 114.2, 115.5, 118.0, 121.3, 124.2, 126.3, 132.5, 133.4, 133.2, 141.1, 159.8, 171.6, 173.3; HRMS calcd for C_{15}H_{19}NO_{2} [M+H]^+: 347.1213. Found: 347.1217.

**General procedure for preparation of 4a-4e**

A mixture of 1a-1e (10 mM), 2 (10 mM) and glycerol (20 ml) was heated for 2-2.5 h. At the end of this period, a colourless solid separated out from reaction mixture which was collected by filtration, washed with hexane (10 ml) and dried. The crude product was recrystallized from a suitable solvent to obtain pure 4a-4e.

**Results and Discussion**

Phthalic anhydride 1a-1e were reacted with 4-aminosalicylic acid 2 in glycerol at 40 °C for 10 min to yield monoacid monoamide derivative i.e 4-(2-carboxybenzamido)-2-hydroxybenzoic acid 3a-3e, respectively.
The latter were each transformed into the corresponding phthalimide 4-(1,3-dioxoisindolin-2-yl)-2-hydroxybenzoic acid 4a-4e in glycerol at 100 °C for 2-2.5 h, involving a dehydrative ring closure, in high yields and in high purity.

Alternatively 4a have been prepared by treatment of 1a and 2 in glycerol at 100 °C for 2 h. The structures of products have been established on the basis of spectral data. (Scheme 1) (Table 1) (Please see experimental section). Then, the reaction of 1a and 2 to form 4a was optimised by carrying out the reaction of 1a (1 mmol) with 2 (1 mmol) in the presence of different solvents (glycerol, ethylene glycol, PEG-600 and DMF) at different temperatures (Table 1). However, reaction with glycerol at 100°C for 2 h, unlike other solvents gave reasonably high yield (85%) of the product 4a (Table 1, entry 3). Thus, glycerol was found to be best solvent for this reaction to form 4a at 100 °C for 2 h. After having optimized the reaction conditions, the generality of the reaction was confirmed by carrying out the condensation of several others 1a-1e with 2 in glycerol as a solvent at 100°C for 2-2.5 h yielding 4a-4e. The structures of the products have been established on the basis of their spectral data. (Scheme 1) (Please see experimental section).

![Scheme 1. Synthesis of 3a-3e and 4a-4e.](image)

<table>
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</table>

**Conclusion**

Facile and green process for the preparation of potential anti-tuberculosis compounds have been developed. These compounds are structural analogues of p-aminosalicylic acid. The overall yields of these compounds are very good.

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**References**


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