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

Y. Dathu Reddy,[a]* P. Praveen Kumar,[a] B. Rama Devi,[a] Ch. Venkata Ramana Reddy[a] and P. K. Dubey[a]

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

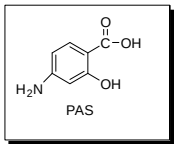
Green synthesis of novel compounds 4-(2-carboxybenzamido)-2-hydroxybenzoic acids **3a-3e** and 4-(1,3-dioxoisoindolin-2-yl)-2-hydroxybenzoic acids **4a-4e** have been developed in good yields which were analogues of *p*-aminosalicylic acid (used as anti-tuberculosis agent).

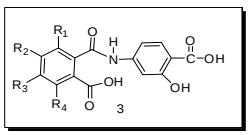
Corresponding Authors
E-Mail: dathureddyjntuh@gmail.com
[a] Department of Chemistry, Jawaharlal Nehru Technological University Hyderabad College of Engineering, Kukatpally, Hyderabad (A.P), India-500 085.

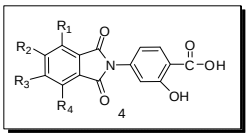
Introduction

Tuberculosis (TB), an infection of *Mycobacterium tuberculosis*, still remains the leading cause of worldwide deaths among infectious diseases.[1] 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.[2] Considering TB problems, the WHO declared this disease a global health emergency in 1993.[3] It is commonly known that *Mycobacterium tuberculosis* has developed resistance to the majority of the existing drugs.[4] 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.[3,5] 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.[5] PAS can cause some side effects including nausea, vomiting, abdominal pain, hepatitis and jaundice.[5] 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 posses beneficial pharmaceutical effects, like analgesic,[6] anti-inflammatory[7] and antiviral,[8] etc.

Keeping the above details/facts in mind and in continuation of our earlier studies,[9] 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

Melting points are uncorrected and were determined in open capillary tubes in sulphuric acid bath. TLC were run on silica gel – G and visualization was done using iodine or UV light. IR spectra were recorded using Perkin – Elmer 1000 instrument in KBr pellets. ^{1}H NMR spectra were recorded in DMSO – d_6 using TMS as internal standard with 400 MH_Z spectrometer. Mass spectra on an Agilent LC-MS instrument.

General procedure for preparation of 3a-3e

A mixture of **1a-1e** (10 mM), **2** (10 mM) and glycerol (20 ml) was heated at 40 ^{o}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 ^{o}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); ^{1}H- NMR (DMSO-d_6, 400 MHz) : δ 7.0 (s, 1H, -NH, D_2O exchangeable), 7.4-8.0 (m, 7H, Ar-H), 10.6 (s, 1H, -OH, D_2O exchangeable), 11.5 (s, 1H, -COOH, D_2O exchangeable) 13.2 (s, 1H, -COOH, D_2O exchangeable); ^{13}C-NMR (DMSO-d_6, 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 $C_{15}H_{11}NO_6$ $[M+H]^+$: 302.5215. Found: 302.5212.

3b: Yield = 3.71 g (85%), M.P: >220 ^oC; 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) ; ^1H- NMR (DMSO-d_6, 400 MHz) : δ 7.2 (s, 1H, -NH, D_2O exchangeable), 7.4-8.0 (m, 3H, Ar-H), 10.4 (s, 1H, -OH, D_2O exchangeable), 11.6 (s, 1H, -COOH, D_2O exchangeable) 13.4 (s, 1H, -COOH, D_2O exchangeable); ^{13}C-NMR (DMSO-d_6, 400 MHz): δ 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 $C_{15}H_7Cl_4NO_6$ $[M+H]^+$: 437.3232. Found: 437.3236.

3c: Yield = 5.12 g (83%), M.P: >220 ^oC; 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) ; ^1H- NMR (DMSO-d_6, 400 MHz): δ 7.2 (s, 1H, -NH, D_2O exchangeable), 7.4-8.0 (m, 7H, Ar-H), 10.4 (s, 1H, -OH, D_2O exchangeable), 11.5 (s, 1H, -COOH, D_2O exchangeable) 13.2 (s, 1H, -COOH, D_2O exchangeable); ^{13}C-NMR (DMSO-d_6, 400 MHz): δ 111.3, 111.9, 112.8, 114.4, 115.0, 117.7, 120.4, 123.4, 124.7, 126.3, 128.3, 136.2, 157.7, 171.0, 175.9; HRMS calcd for $C_{15}H_7Br_4NO_6$ $[M+H]^+$: 617.7313. Found: 617.7317.

3d: Yield = 2.77 g (80%), M.P: >220 ^oC; 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) ; ^1H- NMR (DMSO-d_6, 400 MHz): δ 7.4 (s, 1H, -NH, D_2O exchangeable), 7.4-8.0 (m, 6H, Ar-H), 10.4 (s, 1H, -OH, D_2O exchangeable), 11.7 (s, 1H, -COOH, D_2O exchangeable) 13.4 (s, 1H, -COOH, D_2O exchangeable); ^{13}C-NMR (DMSO-d_6, 400 MHz): δ 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 $C_{15}H_{10}N_2O_8$ $[M+H]^+$: 347.1216. Found: 347.1213.

3e: Yield = 2.77 g (80%), M.P: >220 ^oC; IR (KBr) : 3030-3350 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) ; ^1H- NMR (DMSO-d_6, 400 MHz) : δ 7.4 (s, 1H, -NH, D_2O exchangeable), 7.4-8.0 (m, 6H, Ar-H), 10.5 (s, 1H, -OH, D_2O exchangeable), 11.6 (s, 1H, -COOH, D_2O exchangeable) 13.6 (s, 1H, -COOH, D_2O exchangeable); ^{13}C-NMR (DMSO-d_6, 400 MHz): δ 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 $C_{15}H_{10}N_2O_8$ $[M+H]^+$: 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.**

4a: Yield = 2.41 g (85%), M.P: >220 ^oC; IR (KBr) : 3040-3350 cm^{-1} (broad, medium, -OH groups), 1700 cm^{-1} (sharp, strong, -CO- of acid group), 1690 cm^{-1} (sharp, strong, -CO- of acid group), 1635 cm^{-1} (sharp, strong, -CO- of amide group) ; ^1H- NMR (DMSO-d_6, 400 MHz): 7.4-8.0 (m, 7H, Ar-H), 11.4 (s, 1H, -OH, D_2O exchangeable), 13.6 (s, 1H, -COOH, D_2O exchangeable); ^{13}C-NMR (DMSO-d_6, 400 MHz): δ 110.6, 113.6, 116.5, 116.8, 123.7, 124.9, 126.1, 127.6, 132.7, 134.1, 140.1, 158.0, 158.3, 175.9; HRMS calcd for $C_{15}H_9NO_5$ $[M+H]^+$: 284.3018. Found: 284.3014.

4b: Yield = 3.58 g (85%), M.P: >220 ^oC; IR (KBr) : 3030-3380 cm^{-1} (broad, medium, -OH groups), 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) ; ^1H- NMR (DMSO-d_6, 400 MHz) : 7.4-8.0 (m, 3H, Ar-H), 11.2 (s, 1H, -OH, D_2O exchangeable), 13.4 (s, 1H, -COOH, D_2O exchangeable); ^{13}C-NMR (DMSO-d_6, 400 MHz): δ 112.4, 114.5, 115.5, 116.9, 120.5, 123.3, 125.2, 126.5, 130.4, 133.9, 142.1, 157.8, 158.2, 173.8; HRMS calcd for $C_{15}H_9Cl_4NO_5$ $[M+H]^+$: 422.2116. Found: 422.2119.

4c: Yield = 4.67 g (78%), M.P: >220 ^oC; IR (KBr) : 3035-3350 cm^{-1} (broad, medium, -OH groups), 1705 cm^{-1} (sharp, strong, -CO- of acid group), 1680 cm^{-1} (sharp, strong, -CO- of acid group), 1630 cm^{-1} (sharp, strong, -CO- of amide group) ; ^1H- NMR (DMSO-d_6, 400 MHz) : 7.4-8.0 (m, 3H, Ar-H), 11.6 (s, 1H, -OH, D_2O exchangeable), 13.2 (s, 1H, -COOH, D_2O exchangeable); ^{13}C-NMR (DMSO-d_6, 400 MHz): δ 111.2, 112.5, 115.7, 118.6, 121.7, 122.6, 127.2, 128.8, 131.3, 136.2, 141.5, 156.9, 157.5, 174.3; HRMS calcd for $C_{15}H_9Br_4NO_5$ $[M+H]^+$: 599.1015. Found: 599.1018.

4d: Yield = 2.63 g (80%), M.P: >220 ^oC; IR (KBr) : 3038-3353 cm^{-1} (broad, medium, -OH groups), 1700 cm^{-1} (sharp, strong, -CO- of acid group), 1685 cm^{-1} (sharp, strong, -CO- of acid group), 1620 cm^{-1} (sharp, strong, -CO- of amide group) ; ^1H- NMR (DMSO-d_6, 400 MHz): 7.4-8.0 (m, 6H, Ar-H), 11.0 (s, 1H, -OH, D_2O exchangeable), 13.6 (s, 1H, -COOH, D_2O exchangeable); ^{13}C-NMR (DMSO-d_6, 400 MHz): δ 110.5, 111.9, 113.2, 114.5, 122.8, 123.5, 124.6, 125.7, 130.5, 132.3, 142.8, 158.4, 158.9, 174.6; HRMS calcd for $C_{15}H_8N_2O_7$ $[M+H]^+$: 329.3315. Found: 329.3319.

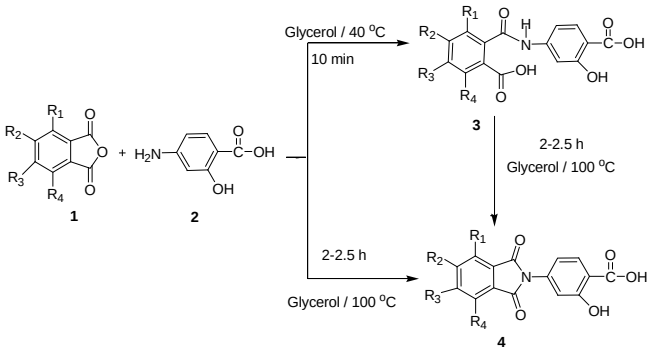
4e: Yield = 2.63 g (80%), M.P: >220 ^oC; IR (KBr) : 3020-3340 cm^{-1} (broad, medium, -OH groups), 1700 cm^{-1} (sharp, strong, -CO- of acid group), 1695 cm^{-1} (sharp, strong, -CO- of acid group), 1625 cm^{-1} (sharp, strong, -CO- of amide group) ; ^1H- NMR (DMSO-d_6, 400 MHz): 7.4-8.0 (m, 6H, Ar-H), 11.0 (s, 1H, -OH, D_2O exchangeable), 13.4 (s, 1H, -COOH, D_2O exchangeable); ^{13}C-NMR (DMSO-d_6, 400 MHz): δ 111.3, 112.4, 114.3, 115.6, 122.4, 124.4, 125.3, 126.8, 133.7, 135.3, 141.2, 157.9, 158.7, 174.8; HRMS calcd for $C_{15}H_8N_2O_7$ $[M+H]^+$: 329.3315. Found: 329.3319.

Results and Discussion

Phthalic anhydride **1a-1e** were reacted with 4-aminosalicylic acid **2** in glycerol at 40 ^oC 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-dioxoisoindolin-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).



1	=	R_1	R_2	R_3	R_4
1a	=	H	H	H	H
1b	=	Cl	Cl	Cl	Cl
1c	=	Br	Br	Br	Br
1d	=	H	NO_2	H	H
1e	=	NO_2	H	H	H

Scheme 1. Synthesis of **3a-3e** and **4a-4e**.

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.

Table 1. Effect of solvent on reaction of **1a** with **2** yielding 4a.

Entry	Solvent	*T*, °C	Time, min	Yield of 4a, %
1	Glycerol	40	6	70
2	Glycerol	80	4	80
3	Glycerol	100	2	85
4	Ethylene glycol	40	6	45
5	Ethylene glycol	80	4	80
6	Ethylene glycol	100	2	80
7	PEG-600	40	6	60
4	PEG-600	80	4	75
5	PEG-600	100	2	80
6	DMF	40	5	60
7	DMF	80	3	70
8	DMF	100	2	75

Acknowledgement

Authors are very thankful to the authorities of **Jawaharlal Nehru Technological University Hyderabad** for providing laboratory facilities and for encourgement.

References

[1]Guzel, O., Terzioglu, N., Capan, G., Salman, A., *Arkivoc*., **2006**(12), 98-110.

[2]Savini, L., Chiasserini, L., Gaeta, A., Pellerano, C., *Biorg. Med. Chem.,* **2002,** *10*, 2193-2198.

[3]Souza, M. V. N. D., *Recent Pat. Antiinfect. Drug. Discov.,* **2006**, *1,* 33-44.

[4]Trivedi, A. R., Dodiya, D. K., Ravat, N. R., Shah, V. H., *Arkivoc.,* **2008**(11), 131-141.

[5]Reed. M. D., Blumer, J. L., *Pediatr. Clin. North Am*., **1983**, *30(1),* 177-193.

[6]Okunrobo, L. O., Usifoh, O. C., Okpo, S. O., *Pak. J. Pharm. Sci.,* **2006**, *19*, 28.

[7]Pandey, V. K., Raj, N., *Curr Sci.,* **1984**, *53*, 256-268.

[8]Alaa, A. M., Abdel, A., *Eur. J. Med. Chem.,* **2007**, *42,* 614-626.

[9](a)Reddy, Y. D., Reddy, Ch. V. R., Dubey, P. K., *RSC Adv.,* **2014**, *4,* 2974-2979; (b) Reddy, Y. D., Kumar, P. P., Devi, B. R., Dubey, P. K., Kumari, Y. B., *Lett. Drug. Des. Discov.,* **2013**, *10*, 226-238; (c) Reddy, Y. D., Kumar, P. P., Devi, B. R., Dubey, P. K., Kumari, Y. B., *Lett. Org. Chem.,* **2013**, *10*, 70-76; (d) Kumar, P. P., Devi, B. R., Dubey, P. K., *Curr. Catal.,* **2012**, *10,* 202-205.

Received: 16.03.2014.
Accepted: 08.04.2014.