

RESEARCH ARTICLE

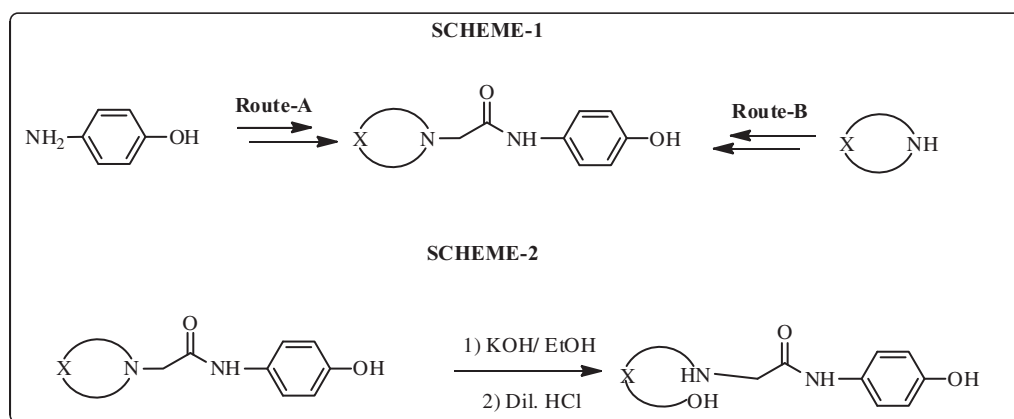
Green approach for drug design and discovery of paracetamol analogues as potential analgesic and antipyretic agents

Y. Dathu Reddy*, Ch. Venkata Ramana Reddy and P.K. Dubey

Department of Chemistry, Jawaharlal Nehru Technological University Hyderabad College of Engineering, Hyderabad, India

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Environmental friendly syntheses of potential analgesic and antipyretic compounds, 2-(1,3-dioxo-1,3-dihydroisoindol-2-yl)-N-(4-hydroxyphenyl)acetamide derivatives **6a–6g** and N-[(4-hydroxy-phenylcarbonyl)-methyl]-phthalamic acid derivatives **10a–10g** have been developed. Two synthetic routes (A and B) have been established for the preparation of **6a–6g**. In route A, 4-aminophenol **2** was reacted with chloroacetyl chloride **3** in a solution of potassium acetate and acetic acid to yield N-(4-hydroxyphenyl)-2-chloroacetamide **4**. The latter was reacted with imide compounds **5a–5g** either in triethanolamine as a green solvent or in solid phase in the presence of triethylbenzylammonium chloride and potassium iodide (KI) to yield **6a–6g**. Alternatively, in route B, the reaction of anhydrides **7a–7g** with glycine **8** yielded the (1,3-dioxo-1,3-dihydroisoindol-2-yl)acetic acid derivatives **9a–9g** which on reaction with **2** either in triethanolamine and dicyclohexylcarbodiimide (DCC) as a dehydrating agent or in solid phase in the presence of DCC gave **6a–6g**. The latter were hydrolysed in 0.5N ethanolic potassium hydroxide (KOH) to afford **10a–10g**.



Keywords: green synthesis; paracetamol analogue compounds; analgesic and antipyretic

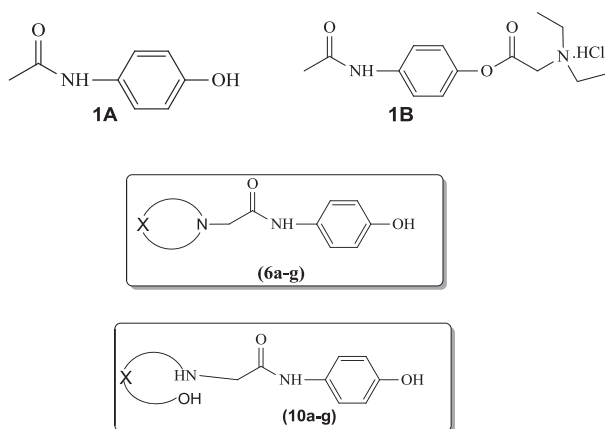
Introduction

Paracetamol is a widely used (*1*) analgesic (pain reliever) and antipyretic (fever reducer) drug. It is commonly used (*1*) for the relief of headaches, other minor aches and pains. Paracetamol can also be used (*1*) in the management of more severe pain such as post-surgical pain and in providing palliative care in advanced cancer patients (*1*), but the lower water solubility is problematic for some delivery applications (*2–4*). A water-soluble analogue of **1** is the prodrug propacetamol hydrochloride **2** (*5*). This form

of paracetamol is rapidly and completely hydrolysed to release **1** (*6*). The pharmacological effects in clinical trials have shown that **2** possesses efficacy similar to that of **1**. However, due to its greater water solubility, it can be parenterally administered and thus be employed when oral administration is not possible (*5*). Phthalimide derivatives have been widely reported to possess beneficial pharmaceutical effects, like analgesic (*7*), antiinflammatory (*8*) and antiviral (*9*) activities. In view of these analgesic and antipyretic properties, it was considered worthwhile to prepare

*Corresponding author. Email: dathureddyjntuh@gmail.com

the phthalimide derivatives of paracetamol **6a–6g** and **10a–10g** which may possess potency equal to that of paracetamol **1** itself.



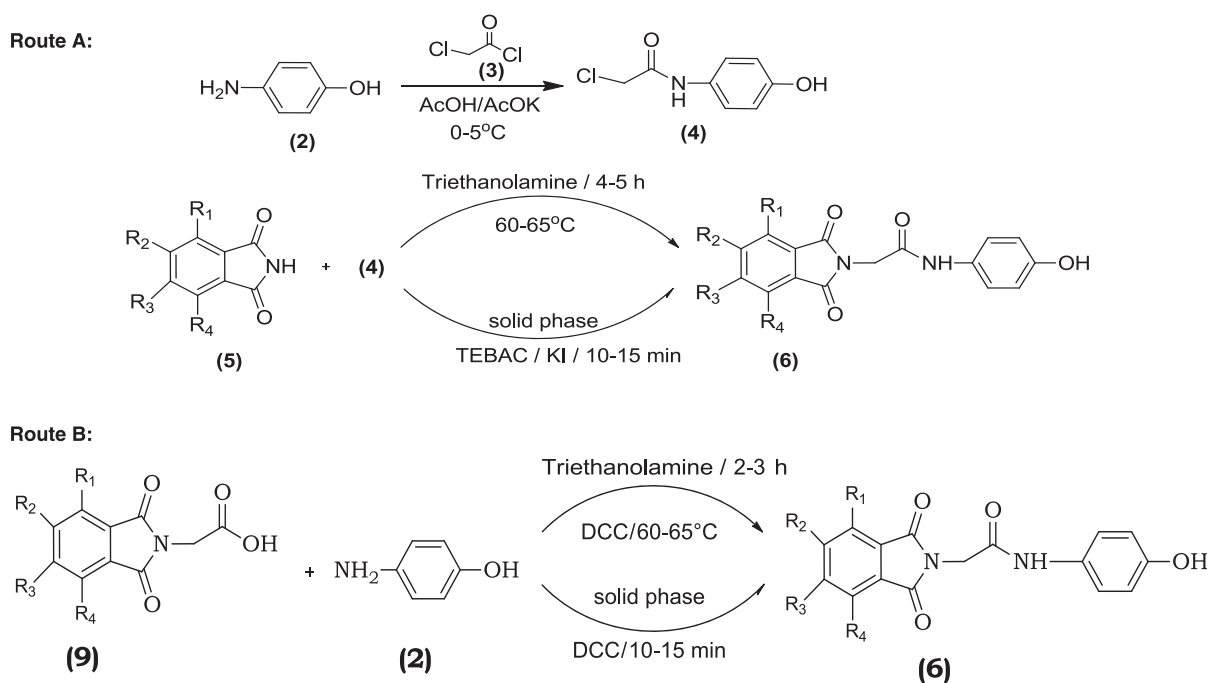
Results and discussion

Two synthetic routes (A and B) have been established for the preparation of **6a–6g**. As illustrated in [Scheme 1](#), the two routes differ primarily in the sequence in which the imide moiety is added to the acetyl unit. In route A, the treatment of 4-aminophenol **2** with chloroacetyl chloride **3** in a solution of acetic acid containing potassium acetate at 0–5 °C for about 30 min resulted in the formation of

N-(4-hydroxyphenyl)-2-chloroacetamide **4**. The latter, on reaction with the imides **5a–5g** in triethanolamine at 60–65 °C for 4–5 hr, yielded **6a–6g**. These reactions have been also done in solid phase by a simple physical grinding of reactants in the presence of triethylbenzylammonium chloride (TEBAC) as surface catalyst and potassium iodide (KI) at room temperature in a mortar and pestle for 10–15 min. Its structure has been established on the basis of spectral and analytical data ([Scheme 1](#), route A) ([Table 1](#)).

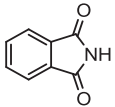
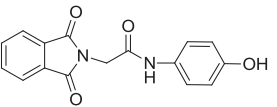
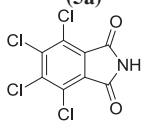
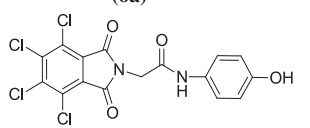
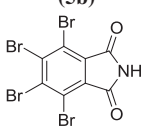
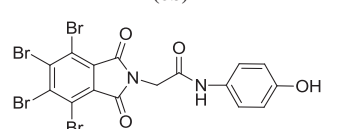
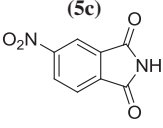
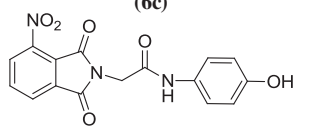
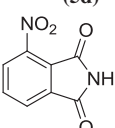
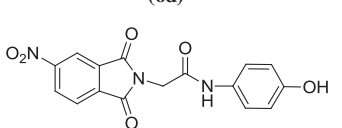
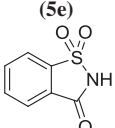
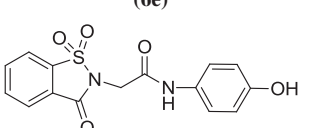
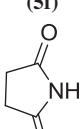
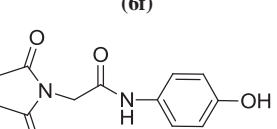
Alternatively, in route B, the treatment of anhydrides **7a–7g** with glycine **8** resulted in the formation of the acid intermediates ([10–13](#)) **9a–9g** which on treatment with **2** either in triethanolamine and dicyclohexylcarbodiimide (DCC) as a catalyst at 60–65 °C for 2–3 hr or in solid phase by a simple physical grinding in the presence of DCC at room temperature for 10–15 min resulted in the formation of **6a–6g**. The melting points of these products were found to be identical with the ones obtained earlier in route A ([Table 2](#)). These reactions are shown in route B of [Scheme 1](#).

Hydrolysis of **6a–6g** was readily achieved with 0.5N ethanolic potassium hydroxide (KOH) followed by treatment with dil. dilute hydrochloric acid (HCl) affording the corresponding acids **10a–10g**. The structures of these products have been established on the basis of spectral and analytical data ([Table 3](#)). These reactions are shown in [Scheme 2](#).



Scheme 1. Synthetic routes to **6a–6g**.

Table 1. Synthesis of **6a–6g** by conventional method by grinding from **5a–5g**.

| Entry | Starting material used | Product obtained | Solution phase (triethanolamine) | | Solid phase | |
|-------|--|--|----------------------------------|--------------------|-------------|--------------------|
| | | | Time (hr) | Yield ^a | Time (min) | Yield ^a |
| 1 |  (5a) |  (6a) | 4 | 75 | 10 | 75 |
| 2 |  (5b) |  (6b) | 4 | 75 | 10 | 70 |
| 3 |  (5c) |  (6c) | 4 | 70 | 10 | 65 |
| 4 |  (5d) |  (6d) | 5 | 65 | 12 | 65 |
| 5 |  (5e) |  (6e) | 5 | 60 | 11 | 65 |
| 6 |  (5f) |  (6f) | 4 | 65 | 15 | 70 |
| 7 |  (5g) |  (6g) | 5 | 70 | 15 | 70 |

Note: ^aYields of crude products only.

Conclusion

Facile and green process for the preparation of potential analgesic and antipyretic compounds, **6a–6g** and **10a–10g** has been developed. These compounds are structural analogues of paracetamol **1A**. The overall yields of these compounds are very good.

Experimental section

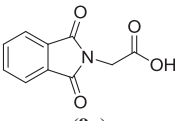
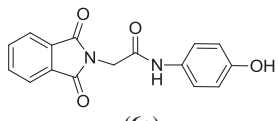
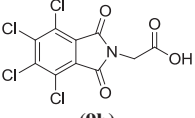
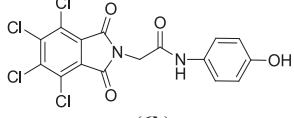
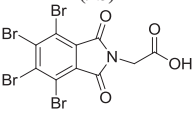
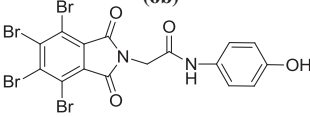
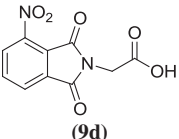
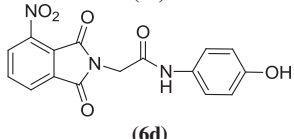
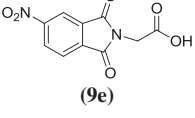
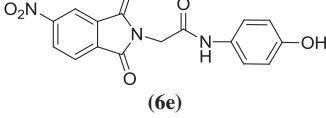
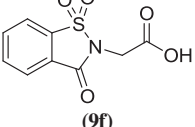
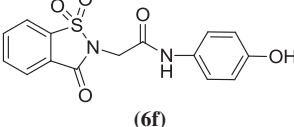
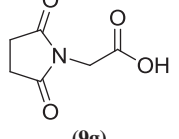
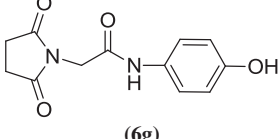
Melting points are uncorrected and were determined in open capillary tubes in sulphuric acid bath. TLC were run on silica gel-G and visualization was done using iodine or UV light. Infrared radiation (IR) spectra were recorded using Perkin–Elmer 1000 instrument in KBr pellets. ¹H NMR spectra were recorded in DMSO-d₆

using tetramethylsilane (TMS) as an internal standard with 400-MHz spectrometer. Mass spectra were recorded on an Agilent-liquid chromatography–mass spectrometry (LCMS) instrument under chemical ionization (CI) conditions and given by *Q*+1 values only.

Preparation of 6a–6g

4 (10 mM), **5a–5g** (11 mM) and triethanolamine (20 ml) were heated at 60–65 °C for 4–5 hr, and then this reaction mixture was cooled to room temperature (RT) and poured into ice-cold water (50 ml). A white solid was separated out which was collected, washed with water (10 ml) and dried. The product was recrystallised from ethanol to obtain **6a–6g**.

Table 2. Synthesis of **6a–6g** by conventional method by grinding from **9a–9g**.

| Entry | Starting material used | Product obtained | Solution phase (triethanol amine) | | Solid phase | |
|-------|--|--|-----------------------------------|--------------------|-------------|--------------------|
| | | | Time (hr) | Yield ^a | Time (min) | Yield ^a |
| 1 |  (9a) |  (6a) | 2 | 75 | 10 | 70 |
| 2 |  (9b) |  (6b) | 2 | 70 | 10 | 75 |
| 3 |  (9c) |  (6c) | 2 | 70 | 10 | 70 |
| 4 |  (9d) |  (6d) | 3 | 65 | 11 | 65 |
| 5 |  (9e) |  (6e) | 3 | 65 | 12 | 65 |
| 6 |  (9f) |  (6f) | 2 | 65 | 12 | 65 |
| 7 |  (9g) |  (6g) | 3 | 70 | 15 | 70 |

Note: ^aYields of crude products only.

Alternative preparation of **6a–6g**

4 (10 mM), **5a–5g** (11 mM) and KI (11 mM) were ground together in a mortar with a pestle for 10–15 min in the presence of TEBC as a surface catalyst. The completion of the reaction was checked by TLC. Then, ice-cold water (20 ml) was added to the reaction mixture, the solid that separated out was filtered, washed with water (10 ml) and dried. The product was recrystallised from ethanol to obtain **6a–6g**.

Preparation of **6a–6g** from **9a–9g**

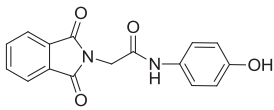
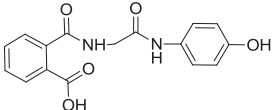
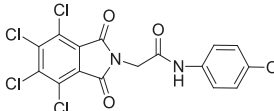
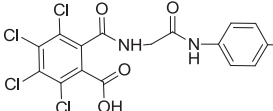
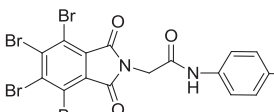
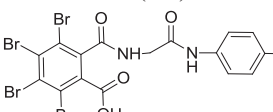
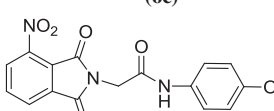
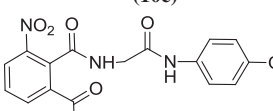
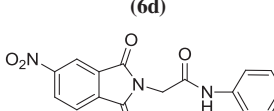
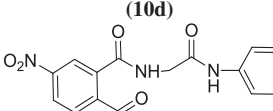
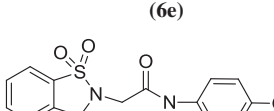
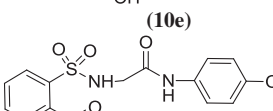
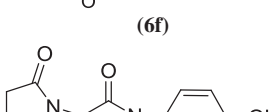
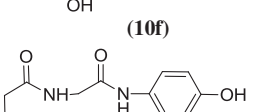
A mixture of **9a–9g** (10 mM), **2** (11 mM), DCC (10 mM) and triethanolamine (20 ml) was heated at 60–65 °C for 2–3 hr. After the completion of the reaction,

the precipitated dicyclohexylurea was collected off and filtrate was poured into ice-cold water (30 ml). The solid that separated out was collected and dried to afford **6a–6g**.

Alternative preparation of **6a–6g** from **9a–9g**

A mixture of **9a–9g** (10 mM), **2** (11 mM) and DCC (10 mM) was ground in mortar by pestle for 10–15 min at RT. The completion of the reaction was checked by TLC. Then ice-cold water (20 ml) was added to reaction mixture, the separated solid was filtered, washed with water (10 ml) and dried. Then washed with CHCl_3 (10 ml) for several times to remove dicyclohexylurea from the product to afford **6a–6g**.

Table 3. Synthesis of **10a–10g** by conventional method by grinding from **6a–6g**.

| Entry | Starting material used | Product obtained | Solution phase (ethanol) | |
|-------|--|---|--------------------------|--------------------|
| | | | Time (hr) | Yield ^a |
| 1 |  (6a) |  (10a) | 1 | 70 |
| 2 |  (6b) |  (10b) | 1 | 70 |
| 3 |  (6c) |  (10c) | 1 | 65 |
| 4 |  (6d) |  (10d) | 1 | 70 |
| 5 |  (6e) |  (10e) | 1 | 65 |
| 6 |  (6f) |  (10f) | 1 | 65 |
| 7 |  (6g) |  (10g) | 1 | 70 |

Note: ^aYields of crude products only.

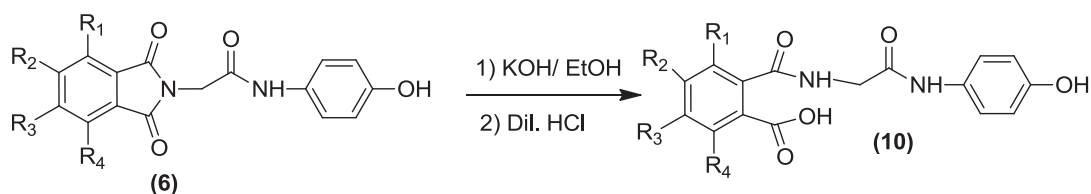
2-(1,3-dioxo-1,3-dihydro-isoindol-2-yl)-N-(4-hydroxyphenyl)acetamide derivatives **6a–6g**

6a: M.P = 215–218 °C; IR (KBr): 3100–3400 cm⁻¹ (broad, medium, –NH– and –OH groups put together), 1665 cm⁻¹ (–C=O of amide group), ¹H NMR (400 MHz, DMSO-d₆/TMS): δ 4.5 (s, 2H, –CH₂), 6.3–8.1 (m, 8H, Ar–H), 8.2 (s, 1H, –OH, D₂O exchangeable), 10.6 (s, 1H, –NH, D₂O exchangeable); M⁺+1 = 297; Anal. Calcd for C₁₆H₁₂N₂O₄ (296.23) C, 64.86; H, 4.08; N, 9.46%, Found: C, 64.82; H, 4.04; N, 9.41%.

6b: M.P = 217–219 °C; IR (KBr): 3100–3400 cm⁻¹ (broad, medium, –NH– and –OH groups put together), 1682 cm⁻¹ (strong, sharp, –CO–); ¹H NMR

(400 MHz, DMSO-d₆/TMS): δ 4.6 (s, 2H, –CH₂), 7–8 (m, 4H, Ar–H), 8.2 (s, 1H, –OH, D₂O exchangeable), 10.6 (s, 1H, –NH, D₂O exchangeable); M⁺+1 = 432; Anal. Calcd for C₁₆H₈Cl₄N₂O₄ (431.13) C, 44.27; H, 1.86; N, 6.45%, Found: C, 44.21; H, 1.82; N, 6.41%.

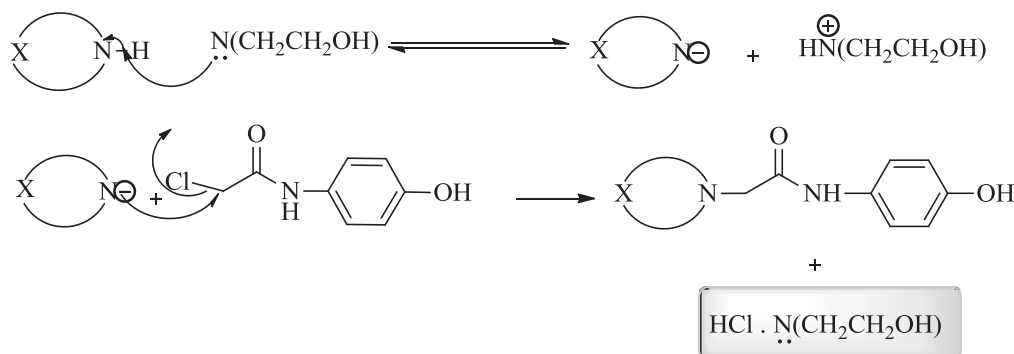
6c: M.P = 210–211 °C; IR (KBr): 3100–3400 cm⁻¹ (broad, medium, –NH– and –OH groups put together), 1662 cm⁻¹ (strong, sharp, –CO–); ¹H NMR (400 MHz, DMSO-d₆/TMS): δ 4.4 (s, 2H, –CH₂), 7–8.4 (m, 4H, Ar–H), 8.4 (s, 1H, –OH, D₂O exchangeable), 10.5 (s, 1H, –NH, D₂O exchangeable); M⁺+1 = 608; Anal. Calcd for C₁₆H₈Br₄N₂O₄ (607.73) C, 31.41; H, 1.32; N, 4.58%, Found: C, 31.47; H, 1.36; N, 4.56%.



| R ₁ | R ₂ | R ₃ | R ₄ |
|-----------------|-----------------|----------------|----------------|
| H | H | H | H |
| Cl | Cl | Cl | Cl |
| Br | Br | Br | Br |
| H | NO ₂ | H | H |
| NO ₂ | H | H | H |

X = -H, C₂H₅

A Plausible mechanism for **6** from **4** & **5**:



Scheme 2. Synthesis of **10a–10g**.

6d: M.P = 205–208 °C; IR (KBr): 3100–3400 cm⁻¹ (broad, medium, -NH- and -OH groups put together), 1662 cm⁻¹ (strong, sharp, -CO-); ¹H NMR (400 MHz, DMSO-d₆/TMS): δ 4.3 (s, 2H, -CH₂), 6.8–8.2 (m, 7H, Ar-H), 8.3 (s, 1H, -OH, D₂O exchangeable), 10.0 (s, 1H, -NH, D₂O exchangeable); M⁺+1 = 342; Anal. Calcd for C₁₆H₁₁N₃O₆ (341.25) C, 56.31; H, 3.25; N, 12.31%, Found: C, 56.34; H, 3.22; N, 12.37%.

6e: M.P = 200–202 °C; IR (KBr): 3100–3400 cm⁻¹ (broad, medium, -NH- and -OH groups put together), 1665 cm⁻¹ (strong, sharp, -CO-); ¹H NMR (400 MHz, DMSO-d₆/TMS): δ 4.2 (s, 2H, -CH₂), 6.8–8.3 (m, 7H, Ar-H), 8.3 (s, 1H, -OH, D₂O exchangeable), 10.0 (s, 1H, -NH, D₂O exchangeable); M⁺+1 = 342; Anal. Calcd for C₁₆H₁₁N₃O₆ (341.25) C, 56.31; H, 3.25; N, 12.31%, Found: C, 56.34; H, 3.22; N, 12.37%.

6f: M.P = 159–160 °C; IR (KBr): 3100–3400 cm⁻¹ (broad, medium, -NH- and -OH groups put together), 1663 cm⁻¹ (strong, sharp, -CO-); ¹H NMR (400 MHz, DMSO-d₆/TMS): δ 4.7 (s, 2H, -CH₂), 6.8–8.4 (m, 8H, Ar-H), 8.4 (s, 1H, -OH, D₂O exchangeable), 10.3 (s, 1H, -NH, D₂O exchangeable); M⁺+1 = 333; Anal. Calcd for C₁₅H₁₂N₂O₅S (332.27) C, 54.21; H, 3.64; N, 8.43%, Found: C, 54.23; H, 3.66; N, 8.49%.

6g: M.P = 195–198 °C; IR (KBr): 3100–3400 cm⁻¹ (broad, medium, -NH- and -OH groups put together), 1681 cm⁻¹ (strong, sharp, -CO-); ¹H NMR (400 MHz, DMSO-d₆/TMS): δ 4.7 (s, 2H, -CH₂), 6.8–7.8 (m, 4H, Ar-H), 2.6 (s, 4H, -CH₂-CH₂-), 8.4 (s, 1H, -OH, D₂O exchangeable), 10.07 (s, 1H, -NH, D₂O exchangeable); M⁺+1 = 249; Anal. Calcd for C₁₂H₁₂N₂O₄ (248.11) C, 58.06; H, 4.87; N, 11.29%, Found: C, 58.02; H, 4.84; N, 11.27%.

Preparation of 10a–10g by hydrolysis of 6a–6g

A mixture of **6a–6g** (10mM) and ethanolic KOH (0.5N) was stirred at RT for 1 hr. Then the solution was acidified with dil.HCl. This solution was extracted with ethyl acetate (20 ml) and separated the organic layer. The organic layer was dried over-anhydrous sodium sulfate and the collected solvent was evaporated to give **10a–10g**.

N-[*(4*-hydroxy-phenylcarbamoyl)-methyl]-phthalamic acid derivatives **10a–10g**

10a: M.P \geq 220 °C; IR (KBr): 3100–3400 cm^{-1} (broad, medium, –NH– and –OH groups put together), 1734 cm^{-1} (strong, sharp, –CO– of acid group), 1665 cm^{-1} (strong, sharp, –CO– of amide group); ^1H NMR (400 MHz, $\text{D}_2\text{O}/\text{TMS}$): δ 4.1 (s, 2H, –CH₂), 6.3–8.1 (m, 8H, Ar–H), 8.4 (s, 1H, –OH, D_2O exchangeable), 10.1 (s, 1H, –NH, D_2O exchangeable), 10.12 (s, 1H, –NH, D_2O exchangeable) 13.06 (s, 1H, –COOH, D_2O exchangeable); $M^+ + 1 = 315$; Anal. Calcd for $\text{C}_{16}\text{H}_{14}\text{N}_2\text{O}_5$ (314.46) C, 61.14; H, 4.49; N, 8.91%; Found: C, 61.17; H, 4.45; N, 8.95%.

10b: M.P \geq 220 °C; IR (KBr): 3100–3400 cm^{-1} (broad, medium, –NH– and –OH groups put together), 1735 cm^{-1} (strong, sharp, –CO– of acid group), 1665 cm^{-1} (strong, sharp, –CO– of amide group); ^1H NMR (400 MHz, $\text{DMSO-d}_6/\text{TMS}$): δ 4.3 (s, 2H, –CH₂), 6.8–8.0 (m, 4H, Ar–H), 8.1 (s, 1H, –OH, D_2O exchangeable), 10.1 (s, 1H, –NH, D_2O exchangeable), 10.3 (s, 1H, –NH, D_2O exchangeable) 13.06 (s, 1H, –COOH, D_2O exchangeable); $M^+ + 1 = 450$; Anal. Calcd for $\text{C}_{16}\text{H}_{10}\text{Cl}_4\text{N}_2\text{O}_5$ (449.26) C, 42.51; H, 2.23; N, 6.20%; Found: C, 42.55; H, 2.26; N, 6.24%.

10c: M.P \geq 220 °C; IR (KBr): 3100–3400 cm^{-1} (broad, medium, –NH– and –OH groups put together), 1734 cm^{-1} (strong, sharp, –CO– of acid group), 1652 cm^{-1} (strong, sharp, –CO– of amide group); ^1H NMR (400 MHz, $\text{DMSO-d}_6/\text{TMS}$): δ 4.7 (s, 2H, –CH₂), 6.8–8.4 (m, 4H, Ar–H), 8.2 (s, 1H, –OH, D_2O exchangeable), 10.07 (s, 1H, –NH, D_2O exchangeable), 10.12 (s, 1H, –NH, D_2O exchangeable) 13.07 (s, 1H, –COOH, D_2O exchangeable); $M^+ + 1 = 626$; Anal. Calcd for $\text{C}_{18}\text{H}_{14}\text{Br}_4\text{N}_2\text{O}_5$ (625.34) C, 30.51; H, 1.60; N, 4.45%; Found: C, 30.53; H, 1.64; N, 4.42%.

10d: M.P \geq 220 °C; IR (KBr): 3100–3400 cm^{-1} (broad, medium, –NH– and –OH groups put together), 1732 cm^{-1} (strong, sharp, –CO– of acid group), 1681 cm^{-1} (strong, sharp, –CO– of amide group); ^1H NMR (400 MHz, $\text{DMSO-d}_6/\text{TMS}$): δ 4.8 (s, 2H, –CH₂), 6.8–8.4 (m, 7H, Ar–H), 8.1 (s, 1H, –OH, D_2O exchangeable), 10.1 (s, 1H, –NH, D_2O

exchangeable), 10.12 (s, 1H, –NH, D_2O exchangeable) 13.07 (s, 1H, –COOH, D_2O exchangeable); $M^+ + 1 = 360$; Anal. Calcd for $\text{C}_{18}\text{H}_{17}\text{N}_3\text{O}_7$ (359.10) C, 53.49; H, 3.65; N, 11.70%; Found: C, 53.44; H, 3.61; N, 11.71%.

10e: M.P \geq 220 °C; IR (KBr): 3100–3400 cm^{-1} (broad, medium, –NH– and –OH groups put together), 1720 cm^{-1} (strong, sharp, –CO– of acid group), 1650 cm^{-1} (strong, sharp, –CO– of amide group); ^1H NMR (400 MHz, $\text{DMSO-d}_6/\text{TMS}$): δ 4.5 (s, 2H, –CH₂), 6.8–8.4 (m, 7H, Ar–H), 8.1 (s, 1H, –OH, D_2O exchangeable), 10.20 (s, 1H, –NH, D_2O exchangeable), 10.3 (s, 1H, –NH, D_2O exchangeable) 13.04 (s, 1H, –COOH, D_2O exchangeable); $M^+ + 1 = 360$; Anal. Calcd for $\text{C}_{18}\text{H}_{17}\text{N}_3\text{O}_7$ (359.10) C, 53.49; H, 3.65; N, 11.70%; Found: C, 53.44; H, 3.61; N, 11.71%.

10f: M.P \geq 220 °C; IR (KBr): 3100–3400 cm^{-1} (broad, medium, –NH– and –OH groups put together), 1720 cm^{-1} (strong, sharp, –CO– of acid group), 1680 cm^{-1} (strong, sharp, –CO– of amide group); ^1H NMR (400 MHz, $\text{DMSO-d}_6/\text{TMS}$): δ 4.7 (s, 2H, –CH₂), 6.8–8.4 (m, 8H, Ar–H), 8.1 (s, 1H, –OH, D_2O exchangeable), 10.07 (s, 1H, –NH, D_2O exchangeable), 10.12 (s, 1H, –NH, D_2O exchangeable) 13.07 (s, 1H, –COOH, D_2O exchangeable); $M^+ + 1 = 351$. Anal. Calcd for $\text{C}_{17}\text{H}_{18}\text{N}_2\text{O}_6\text{S}$ (350.08) C, 51.42; H, 4.03; N, 8.00%; Found: C, 51.45; H, 4.07; N, 8.04%.

10g: M.P \geq 220 °C; IR (KBr): 3100–3400 cm^{-1} (broad, medium, –NH– and –OH groups put together), 1720 cm^{-1} (strong, sharp, –CO– of acid group), 1650 cm^{-1} (strong, sharp, –CO– of amide group); ^1H NMR (400 MHz, $\text{DMSO-d}_6/\text{TMS}$): δ 2.54 (t, 2H, –CH₂), 2.7 (t, 2H, –CH₂), 4.7 (s, 2H, –CH₂), 6.8–8 (m, 4H, Ar–H), 8.4 (s, 1H, –OH, D_2O exchangeable), 10.07 (s, 1H, –NH, D_2O exchangeable), 10.12 (s, 1H, –NH, D_2O exchangeable) 13.07 (s, 1H, –COOH, D_2O exchangeable); $M^+ + 1 = 267$; Anal. Calcd for $\text{C}_{14}\text{H}_{18}\text{N}_2\text{O}_5$ (266.12) C, 54.13; H, 5.03; N, 10.52%; Found: C, 54.15; H, 5.06; N, 10.52%.

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