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Synthesis and biological studies of acridine derivatives-based imidazolium salt.

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1. General Experimental

Melting points were measured on an Electrothermal melting point apparatus. Proton and Carbon-13 nuclear magnetic resonance spectra were recorded on a Bruker Avance and a Joel 400 spectrometer at 400 MHz. Chemical shifts are reported as δ values in parts per million (ppm) relative to tetramethylsilane (TMS). Elemental analyses (%CHN) were conducted on a Perkin Elmer 2400 series. Thin layer chromatography was carried out on pre-coated silica gel plates (silica 60 F₂₅₄, Merck). Starting materials and reagents used in reactions were obtained from Merck and Sigma Aldrich, and used without purification, unless otherwise indicated.

2. Experimental Procedures and Analytical Data

2.1 2-Phenylamino benzoic acid

A mixture of 2-chlorobenzoic acid or a derivative (38 mmol), aniline or a derivative (49 mmol), potassium iodide (0.25 mmol, 41 mg) and copper powder (2.0 mmol, 120 mg) in 40 mL DMF was slowly treated with dry potassium carbonate (43 mmol, 6.0 g), and the reaction was refluxed for 6 to 8 hours. After cooling to room temperature the reaction mixture was poured into 30 mL of water and decolorized with charcoal. The mixture was filtered through celite and the filtrate was acidified with concentrated hydrochloric acid (HCl, 1 M) (pH was adjusted to 1-2). The precipitating product was filtered and subsequently dissolved in 100 mL of 5% aqueous sodium carbonate solution (stirring 20 min). The solution was filtered through celite and the purified product was obtained by precipitation with acid as described above. **2-Phenylamino benzoic acid** and its derivatives were obtained as off-white solids.

2.2 9-Chloroacridine and derivatives

2-Phenylamino benzoic acid or a derivative (19 mmol) and phosphorus oxy chloride (POCl₃) (40 ml) were added into a dried round bottom flask and heated slowly on a water bath to 85-90 °C for 15 min. The reaction was monitored carefully; if it turned too violent, the reaction was temporary placed in a cold-water bath until the boiling subsided. After the initial exothermic reaction had seized, the flask was immersed into an oil bath. The temperature was raised to 135-140 °C and the reaction was kept under reflux for 3 h. Excess of phosphorus oxy chloride was subsequently removed by

distillation at 140-150 °C under vacuum. The cooled reaction mixture was poured into a stirred mixture of 25 ml concentrated aqueous ammonia and 13 g of crushed ice. The 9-chloroacridines precipitated within 30 min. They were filtered, washed with saturated sodium carbonate and with water, dried and recrystallized from ethanol to form needle-shaped crystals (**3a-3c**).



Synthesis of 9-chloroacridines

2.2 Synthesis of N-substituted imidazoles

To a solution of imidazole (16 mmol) in THF (60 mL) was added alkyl bromide (14 mmol) and the reaction was stirred at room temperature for about 48 h. NaOH pellets (18 mmol) were added to the mixture and stirring was continued for another 12 h. The reaction mixture was filtered and extracted twice with CH₂Cl₂ against water. The organic phase was dried over anhydrous MgSO₄ and the solvent was removed on a rotary evaporator. The pure N-substituted imidazoles were obtained as yellow liquids.

9-Chloroacridine (3a)



Compounds **3a** was prepared according to previous reports [1-4]. A mixture of 2-phenylamino-benzoic acid (4.0 g, 19 mmol) and POCl₃ (40 mL) was heated slowly in an oil bath to 85-90 °C for 15 min. The temperature was subsequently increased to 135-140 °C, and the reaction was kept at reflux for 3 hr. After the completion of the reaction, excess phosphorous oxychloride was removed by vacuum distillation. The reaction mixture was cooled to room temperature and poured into a stirred mixture of 25 ml concentrated ammonia and crushed ice. The crude 9-chloroacridine precipitated within 30 min. The precipitate was filtered by suction, washed three times with saturated NaHCO₃ and subsequently with water. The precipitate was dried and recrystallized from ethanol to furnished **3a** as pale brown crystals. Yield: 90 %; mp 115-120 °C. FTIR (v cm⁻¹): 3057, 2995 (C-H), 1554, 1467 (C=C), 757 (C-Cl). ¹H NMR (CDCl₃) δ 8.4 (d, 2H, *J*=8 Hz), 8.26 (d, 2H, *J*=8 Hz), 7.85–7.81 (m, 2H), 7.68-7.64 (m, 2H). ¹³C NMR (CDCl₃) δ 148.9, 141.5, 130.8, 129.8, 127.1, 124.8, 124.4.

9-Chloro-2-methoxyacridine (3b)



Compound **3b** was prepared according to previous reports [1-4] following the same method that was applied for compound **3a**. A mixture of 2-(4-methoxyphenylamino)-benzoic acid (4.57 g, 19 mmol) and POCl₃ (40 mL) was heated slowly in oil bath to 85-90 °C for 15 min. The temperature was subsequently increased to 135-140 °C, and the reaction was kept at reflux for 3 hr. After the completion of the, excess phosphorous oxychloride was removed by vacuum distillation. The reaction mixture was cooled to room temperature and poured into a stirred mixture of 25 ml concentrated ammonia and crushed ice. Crude **3b** precipitated within 30 min. The precipitate was filtered by suction, washed three times with saturated NaHCO₃ and subsequently with water. The precipitate was dried over phosphorus pentoxide and recrystallized from ethanol to furnished **3b** as brown crystals. Yield: 95%; mp 160-165 °C. ¹H NMR (CDCl₃) δ 8.40(d, 1H, *J*=8 Hz). 8.32 (d, 1H, *J*=12 Hz), 8.14 (d, 1H, *J*=8 Hz), 7.79-7.75

(m, 1H), 7.67-7.63 (m, 1H), 7.54–7.49 (m, 2H), 4.05 (s, 3H, OCH₃). ¹³CNMR (CDCl₃) δ 158.2, 147.3, 146.2, 138.2, 131.5, 129.8, 129.4, 127.1, 126.0, 125.3, 124.5, 124.2, 99.9, 55.7.

6,9-Dichloro-2-methoxyacridine (3c)



Compound **3c** was prepared according to previous reports [1-4] following same method that was applied for compound **3a**. A mixture of 4-chloro-2-(4-methoxyphenylamino)-benzoic acid (5.21 g, 19 mmol) and POCl₃ (40 mL) was heated slowly in oil bath to 85-90 °C for 15 min. The temperature was subsequently increased to 135-140 °C, and the reaction was kept at reflux for 3 hr. After the completion of the reaction, excess phosphorous oxychloride was removed by vacuum distillation. The reaction mixture was cooled to room temperature and poured into a stirred mixture of 25 ml concentrated ammonia and crushed ice. Crude **3c** precipitated within 30 min. The precipitate was filtered by suction, washed three times with saturated NaHCO₃ and subsequently with water. It was dried over phosphorus pentoxide and recrystallized from ethanol to furnished **3c** as a yellow powder. Yield: 92%; mp 160-165 °C [5]. ¹H NMR (CDCl₃) δ 8.23 (d, 1H, *J*=9 Hz) 8.13 (s, 1H), 8.03 (d, 1H, *J*=8 Hz), 7.47 (t, 2H, *J*=8 Hz), 7.39 (s, 1H), 3.99 (s, 3H, OCH₃). ¹³C NMR (CDCl₃) δ 158.5, 146.6, 146.2, 138.9, 135.9, 131.1, 128.4, 127.8, 126.9, 125.7, 125.3, 122.8, 99.9, 55.9.

9-(1-Imidazolyl) acridine (6a)

FTIR: v (ATR, cm⁻¹) 3090 (C–H), 1629 (C=N), 1555, 1478, 1421 (C=C). ¹H NMR (CDCl₃): δ 8.35 (t, 1H, *J*=1 Hz), 8.32 (t, 1H, *J*=1 Hz), 7.88-7.84 (m, 3H), 7.60-7.59 (m, 4H), 7.49 (t, 1H, *J*=1 Hz), 7.36 (t, 1H, *J*=1 Hz). ¹³C NMR (CDCl₃): 149.2, 139.0, 138.3, 130.7, 130.1, 129.8, 127.6, 122.9, 122.5, 122.3. Anal. calcd. for C₁₆H₁₁N₃: C 78.35, H 4.52, N 17.13 %, found: C 78.31, H 4.54, N 17.15%.

6-Chloro-9-(1-imidazolyl)-2-methoxyacridine (6c)

FTIR: v (ATR, cm⁻¹) 3095 (C–H), 1633 (C=N), 1560, 1475, 1421 (C=C). ¹H NMR (CDCl₃): δ 8.33 (d, 1H, *J*= 1 Hz), 8.22 (d, 1H, *J*=8 Hz), 8.04 (s, 1H), 7.59-7.51(m, 3H), 7.43 (s, 1H), 7.41 (s, 1H), 6.57 (d, 1H, *J*=4 Hz), 3.84 (s, 3H, OCH₃). ¹³C NMR (CDCl₃): δ 159.2, 147.3, 147.2, 136.2, 135.8, 131.5, 130.1, 129.3, 128.3, 127.1, 124.3, 123.4, 121.7, 97.2, 55.8. Anal. calcd. for C₁₇H₁₂ClN₃O: C 65.92, H 3.90, N 13.57 %; found: C 65.90, H 3.91, N 13.59 %.



Overview on N-substituted imidazolium-acridine salts

References

- 1. X. Lang, L. Li, Y. Chen, Q. Sun, Q. Wu, F. Liu, C. Tan, H. Liu, C. Gao, Y. Jiang, Novel synthetic acridine derivatives as potent DNA-binding and apoptosis-inducing antitumor agents. *Bioorganic & Medicinal Chemistry*, 2013. **21**(14), 4170-4177.
- 2. R. Csuk, A. Barthel, and C. Raschke, Convenient access to substituted acridines by a Buchwald–Hartwig amination. *Tetrahedron*, 2004. **60**(27), 5737-5750.
- 3. V. Nadaraj, S.T. Selvi, and S. Mohan, Microwave-induced synthesis and antimicrobial activities of 7,10,11,12-tetrahydrobenzo[c]acridin-8(9H)-one derivatives. *European Journal of Medicinal Chemistry*, 2009. **44**(3), 976-980.
- 4. B. Li, C.-M. Gao, Q.-S. Sun, L.-L. Li, C.-Y. Tan, H.-X. Liu, Y.-Y. Jiang, Novel synthetic acridine-based derivatives as topoisomerase I inhibitors. *Chinese Chemical Letters*, 2014. **25**(7), 1021-1024.
- 5. M. Staderini, M.L. Bolognesi, and J.C. Menéndez, Lewis acid-catalyzed generation of C-C and C-N bonds on π -deficient heterocyclic substrates. *Advanced Synthesis & Catalysis*, 2015, **357**(1), 185-195.























































































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Figure. S 51. UV-Vis spectrum of compounds