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Solvatochromic behaviour and larvicidal activity of acridine-3-carboxylates

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ABSTRACT

A new series of substituted ethyl 10-chloro-4-(3,4-dimethoxyphenyl)-2-hydroxy-12-phenyl-1,4,5,6-tetrahydrobenzo[*a*]acridine-3-carboxylates, **3a–e** have been synthesized through NaOH base mediated cyclocondensation of (*E*)-7-chloro-2-(3,4-dimethoxybenzylidene)-9-phenyl-3,4-dihydroacridin-1(2*H*)-ones, **1a–e** with ethyl acetoacetate. Structures of these synthesized molecules were studied by FT-IR, ^{1}H NMR, ^{13}C NMR and EI-MS. And all the synthesized compounds were evaluated for their UV-absorption studies with various metal solutions. Acridine-3-carboxylate derivatives were tested against fourth instar larvae of *Anopheles stephensi* and *Hippobosca maculata.* Among those compounds, **3b** and **3e** have good larvicidal activities against both *A. stephensi* and *H. maculata.* Toxicity of compounds, **3b** and **3e** compounds were evaluated with the reference non-target aquatic species like, *Sphaerodema annulatum* Fabricius (Heteroptera: Belostomatidae) and *Zyxomma petiolatum* Rambur (Odonata: Libellulidae) results very low LC_{50} values revels that, the synthetic compounds are non toxic.

1. Introduction

Chemical structure and physical properties of compound exhibits different solvatochromism. The chromophore, auxochrome and solvent molecules determine the strength of the intermolecular solute and solvent interactions in the ground state and excited state [1]. Hydrogen bonding, complexation, acid base chemistry, and charge transfer interactions are the specific interactions between the chromophores and solvents. Among these, complexation of metal carboxylate has been extensively studied because the carboxylate group can bind to metal ion in various modes, such as monodentate, bidentate and bridging [2]. Carboxylate and phenolic hydroxyl of salicylate forming strong intramolecular O···H—O hydrogen bond [3]. Cyclohexane carboxylates are salicylic acid derivatives exist as a strong intramolecular hydrogen bonding C═O···OH provides the possibility of intramolecular proton transfer in the lowest existed state of these compounds and determines specific feature of their fluorescence spectra [4–6]. Synthesis of a simple molecule with different functionalities of heterocycles is a worthwhile contribution in the chemistry of heterocycles. Cyclohexanes are either prepared from natural sources or entirely *via* synthetic routes. The reason for their preparation is a variety of medical effects. These kinds of molecules provide anti-convulsant, anti-malarial, anti-inflammatory and cardiovascular effects [7]. Cyclohexanes are also important intermediates for many biologically active compounds [8]. A number of their derivatives have fungicidal and antitumor activities [9]. The chalcones undergo Michael type of reactions with ethyl acetoacetate to afford a variety of products [10–16] depending on the experimental conditions. Mosquitoes are the principal vector of many vector-borne diseases affecting human beings and animals, in addition to nuisance. The World Health Organization estimates that around 2.5 billion people have been infected with dengue vector and this number of viral infection has increased with increase in urbanization. No effective drug or vaccine is available so far. The only solution is to prevent the disease-carrying mosquito from breeding and biting humans [17]. The dengue viral diseases, dengue fever or dengue hemorrhagic fever, and dengue shock syndrome are caused by dengue virus (*Flavivirus*; *Flaviviridae*) by transmitting the vector, *Aedes* species [18]. The mosquito borne diseases can be prevented by killing the mosquitoes, and larvicides are known to play a vital role in controlling them in their breeding sites. (*E*)-2-(benzylidine-7-chloro-9-phenyl 3, 4-dihydroacridin-1(2*H*)-one and its derivatives having good larvicidal activity reported by our research group earlier [19].

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On the basis of these physical, chemical and biological importance of carboxylates, our aim is to prepare a functional group contain carboxylate acridine heterocyclic. In this present study deals with synthesis, spectral characterization, solvatochromism behaviour and larvicidal activity of ethyl 10-chloro-4-(3,4-dimethoxyphenyl)-2-hydroxy-12-phenyl-1,4,5,6-tetrahydro benzo[*a*]acridine-3-carboxylates against fourth instar larvae of *Anopheles stephensi* and *Hippobosca maculata* mosquito larvae.

2. Experimental

2.1. Materials and instrumentation

All commercially available reagents were used without any further purification and the reactions were monitored by TLC. IR spectrum was recorded on a SHIMADZU Infrared spectrophotometer (400–4000 cm^{-1}; resolution: 1 cm^{-1}) using KBr pellets. ^1H and ^{13}C NMR were obtained using a Bruker Avence 400 MHz spectrometer in $CDCl_3$ solution with TMS as an internal standard. Chemical shift values (δ) were given in ppm. Melting points were measured on Elche Microprocessor based DT apparatus using an open capillary tube and are corrected with standard benzoic acid. Exact mass measurements of the molecular ions were obtained on an ESI-MS thermo fleet.

2.2. General procedure for synthesis of ethyl 10-chloro-4-(3,4-dimeth oxyphenyl)-2-hydroxy-12-phenyl-1,4,5,6-tetrahydrobenzo[a]acridine -3-carboxylates, **3a–e**

(*E*)-7-chloro-2-(3,4-dimethoxybenzylidene)-9-phenyl-3,4-dihy droacridin-1(2*H*)-ones, **1a–e** were synthesized by a known procedure [20]. Samples were matched with authenticated report. (*E*)-7-chloro-2-(3,4-dimethoxybenzylidene)-9-phenyl-3,4-dihydro acridin-1(2*H*)-ones analogous, **1a–e** (3 mmol) and ethyl acetoacetate **2** (0.39 g, 0.40 mL, 3 mmol) were refluxed for 5–6 h in presence of 10% ethanolic NaOH. The reaction mixture was poured into good stirring ice-cold water and kept at room temperature until the reaction product separated as a solid, which was filtered off and recrystallized from ethanol. Synthetic pathway was elaborated in Scheme 1 and synthesized derivatives and physical data of all synthesized compounds, **3a–e** were summarized in Table 1. The structures of all the compounds were determined by IR, EIMS, ^1H and ^{13}C NMR and their physical and spectroscopic data are shown below:

2.2.1. Ethyl 10-chloro-4-(3,4-dimethoxyphenyl)-2-hydroxy-12-phenyl -1,4,5,6-tetrahydro benzo[a]acridine-3-carboxylate, **3a**

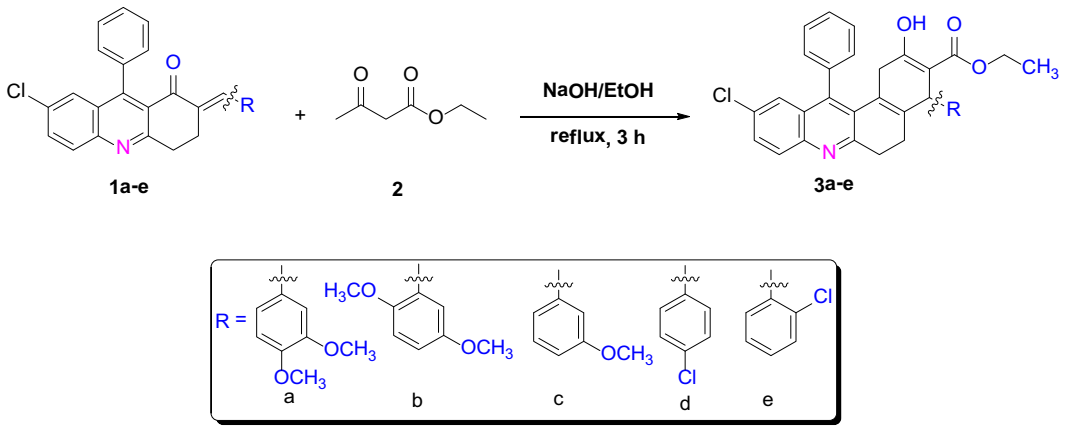
Yellow solid; M.F: $C_{34}H_{30}ClNO_5$; Yield 75%; M.P: 115–117 °C; FT-IR (KBr pellet) ν_{max}/(C m^{-1}): 1666 cm^{-1} (—C=O), 3452 (—OH_{str}); ^1H NMR (400 MHz, $CDCl_3$): δ (ppm), 1.18–1.22 (t, *J* = 6.8 Hz, 3H, —CH_3), 2.29 (s, 2H, —CH_2), 2.40–2.55 (m, 2H, —CH_2), 3.06 (m, 2H, —CH_2), 3.85 (s, 3H, —OCH_3), 3.92 (s, 3H, —OCH_3), 4.09 (q, *J* = 11.2 Hz, 2H, —CH_2), 4.31 (s, 1H, —CH), 6.31 (s, 1H), 6.75 (s, 2H), 7.20–7.22 (d, *J* = 8 Hz, 1H), 7.40 (s, 1H), 7.48–7.54 (m, 1H), 7.57–7.63 (m, 2H), 7.92 (m, 1H), 7.99 (s, 1H), 8.04 (s, 1H), 12.06 (s, 1H, —OH); ^{13}C NMR (400 MHz, $CDCl_3$): δ (ppm), 14.24, 27.85, 33.45, 48.19, 55.87, 60.62, 99.65, 110.96, 111.27, 120.77, 122.69, 125.10, 2 × 127.76, 128.11, 128.47, 128.64, 128.88, 129.00, 129.76, 3 × 129.9, 130.41, 131.92, 136.22, 137.67, 141.46, 141.98, 147.98, 148.87, 160.44, 169.34, 171.28; Exact Mass:567.18; Found ESI-MS *m*/*z* 568.42 [M + 1].

2.2.2. Ethyl 10-chloro-4-(2,5-dimethoxyphenyl)-2-hydroxy-12-phenyl -1,4,5,6-tetrahydro benzo[a]acridine-3-carboxylate, **3b**

Pale yellow solid; M.F: $C_{34}H_{30}ClNO_5$; Yield 73%; M.P: 145–147 °C; FT-IR (KBr pellet) ν_{max}/(C m^{-1}): 1732 (—C=O), 3452 (—OH_{str}). ^1H NMR (400 MHz, $CDCl_3$): δ (ppm), 1.05–1.09 (t, *J* = 6.4 Hz, 3H, —CH_3), 2.20–2.24 (m, 2H, —CH_2), 2.45 (s, 2H, —CH_2), 2.96–3.05 (m, 2H, —CH_2), 3.76 (s, 3H, —OCH_3), 3.80 (s, 3H, —OCH_3), 3.98–4.02 (q, *J* = 11.2 Hz, 2H, CH_2), 4.92 (s, 1H, —CH), 6.54 (s, 1H), 6.66–6.69 (d, *J* = 8.8 Hz, 1H), 6.75–6.78 (d, *J* = 8.4 Hz, 1H), 7.15 (s, 1H), 7.19–7.20 (d, *J* = 7.2 Hz, 1H), 7.39 (s, 1H), 7.44–7.46 (m, 1H), 7.50–7.52 (m, 1H), 7.59–7.61 (m, 1H), 7.89–7.91 (d, *J* = 8.8 Hz, 1H), 7.98 (s, 1H), 12.09 (s, 1H, —OH); ^{13}C NMR (400 MHz, $CDCl_3$): δ (ppm), 13.98, 26.82, 33.46, 41.12, 56.25, 60.36, 98.82, 111.57, 111.99, 115.69, 122.53, 125.10, 126.87, 127.93, 128.05, 128.12, 128.47, 128.68, 129.54, 129.98, 130.06, 130.33, 131.73, 132.73, 133.30, 137.72, 141.18, 141.79, 144.01, 151.71, 153.73, 160.80, 170.13, 171.40; Exact Mass: 567.18; Found EI-MS *m*/*z* 568.42 [M + 1].

2.2.3. Ethyl 10-chloro-2-hydroxy-4-(3-methoxyphenyl)-12-phenyl-1,4,5,6-tetrahydrobenzo [a]acridine-3-carboxylate, **3c**

Yellow solid; M.F: $C_{33}H_{28}ClNO_4$; Yield 71%; M.P: 140–142 °C; FT-IR (KBr pellet) ν_{max}/(C m^{-1}): 1666 (—C=O), 3439 (—OH_{str}); ^1H NMR (400 MHz, $CDCl_3$): δ (ppm), 1.16–1.19 (t, *J* = 6.8 Hz, 3H, —CH_3), 2.30 (s, 2H, —CH_2), 2.46–2.48 (m, 2H, —CH_2), 3.04–3.09 (m, 2H, —CH_2), 3.78 (s, 3H, —OCH_3), 4.06–4.09 (q, *J* = 5.8 Hz, 2H, CH_2), 4.34 (s, 1H, —CH), 6.70 (m, 3H), 6.73–6.77 (m, 1H), 7.15–7.18 (t, *J* = 15.2 Hz, 1H), 7.21–7.25 (m, 1H), 7.42 (s, 1H), 7.45–7.47 (d, *J* = 6.8 Hz, 1H), 7.51–7.53 (m, 1H), 7.57 (s, 1H), 7.60–7.62 (d, *J* = 8 Hz, 1H), 7.90–7.92 (d, *J* = 9.2 Hz, 1H), 13.28 (s, 1H, —OH); ^{13}C NMR (400 MHz, $CDCl_3$): δ (ppm), 14.17, 27.84, 33.61, 48.59, 55.25, 60.61, 99.46, 111.84, 114.40, 120.97, 123.11, 125.10, 2 × 127.74, 128.60, 128.93, 129.06, 129.24, 2 × 129.70, 129.99, 130.02, 130.29, 131.86, 137.60, 141.45, 141.70, 144.11, 145.40,



Scheme 1. Synthesis of ethyl 10-chloro-4-(3,4-dimethoxyphenyl)-2-hydroxy-12-phenyl-1,4,5,6-tetrahydrobenzo[*a*]acridine-3-carboxylates, **3a–e**.