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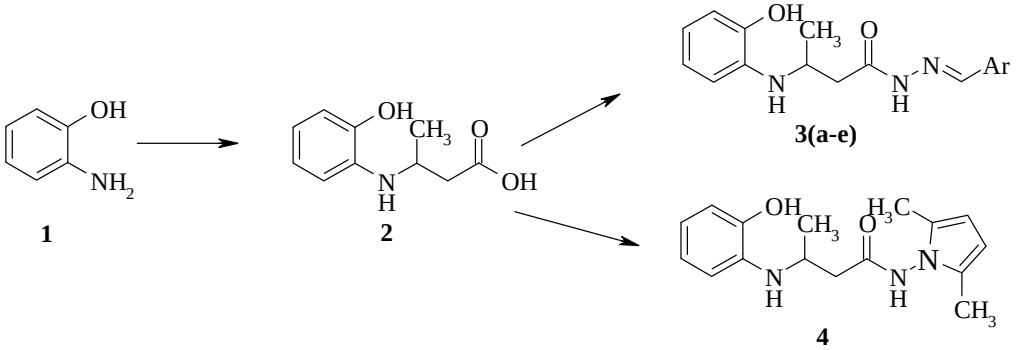
Synthesis, structure and properties of naphthoquinone derivatives, containing amino acid and heterocyclic moieties

The quinone moiety is an important part of many biologically active natural products and their synthetic analogues [1,2]. Natural and synthetic quinones exhibit a variety of biological activities such as cytotoxic, antiviral, anti-inflammatory, antimalarial, antibacterial, antifungal and antiproliferative [3-7] properties. Various 2,3-disubstituted 1,4-naphthoquinone derivatives can be prepared from 2,3-dichloro-1,4-naphthoquinone by its reactions with amino- andhydroxy substituted compounds.

In this work, we describe synthesis of new potentially biologically active 1,4-naphthoquinone derivatives containing heterocyclic moieties. The target compounds were synthesized as illustratedin Schemes 1 and 2. 3-[(2-Hydroxyphenyl)amino]butanoic acid **2** was synthesized from 2-aminophenol with crotonic acid under reflux in water. 3-[(2-Hydroxyphenyl)amino]butanehydrazide was synthesized from acid **2** in toluene with an excess of hydrazine hydrate. Condensation of carbohydrazide with aromatic aldehydes and 2,5-hexanedione gave corresponding 3-[(2-hydroxyphenyl)amino]-*N*-aryl(or furan-2-yl)methylidene]butanehydrazide**3a-e** and *N*-(2,5-dimethyl-1*H*-pyrrol-1-yl)-3-[(2-hydroxyphenyl)amino]butanamide **4** (Scheme 1). The formation of heterocyclic system in compound **4** has been confirmed by the characteristic ^{1}H-NMR peak signal at 5.61 ppm attributed to the protons of two CH groups in the dymethylpyrrole moiety.

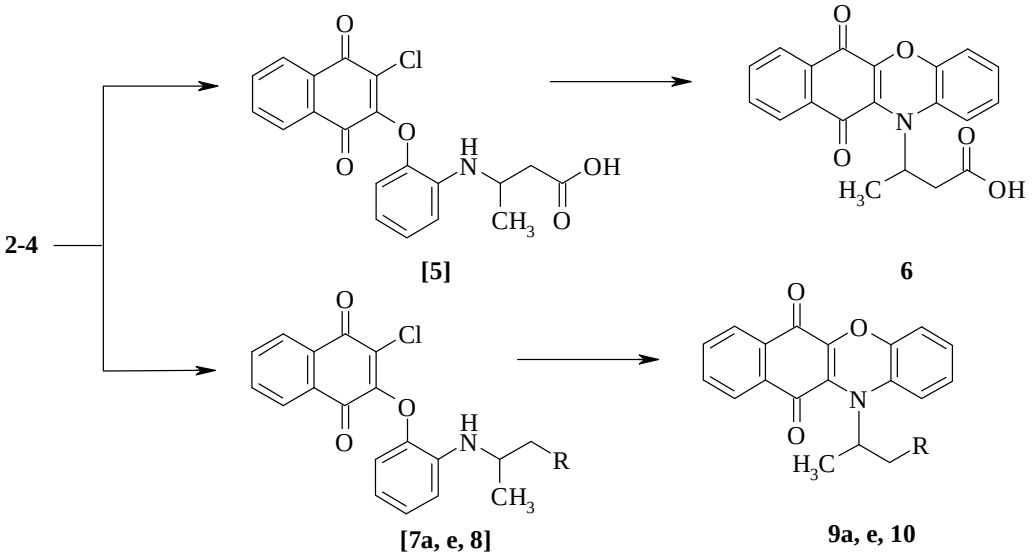
Scheme 1



Ar = **a)** C_6H_5; **b)** 4-H_3CO-C_6H_4; **c)** 4-NO_2-C_6H_4; **d)** 4-F-C_6H_4; **e)** 

3-(6,11-Dioxo-6*H*-benzo[*b*]phenoxazin-12(11*H*)-yl)butanoic acid **6** and *N*-substituted-3-(6,11-dioxo-6*H*-benzo[*b*]phenoxazin-12(11*H*)-yl)butanamide **9a,e** and**10** were obtained by stirring the mixture of the respective compound **2**, **3a,e**or**4**, 2,3-dichloro-1,4-naphthoquinone, and sodium carbonate as a base in dimethyl sulfoxide at room temperature for 14 h (Scheme 2). The reaction was quenched by diluting the reaction mixture with water, causing the products to precipitate.The crude product **6** was purified by acidifying filtrate with acetic acid up to pH 6.

Scheme 2



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