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Synthesis of new derivative of 2-[2-(1H-indol-1-yl)ethyl]-6-phenyl-4,5-dihydropyridazin-3(2H)-one

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Abstract. Pyridazinone hold considerable interest relative to the preparation of organic intermediates and physiologically active compounds (21-25). Various structural modifications were carried out in pyridazinone ring system. These structural changes resulted in some fruitful biological activities of the compounds. In conclusion, we have developed a simple and efficient method for the synthesis of pyridazinones containing compounds. We also believe that the procedural simplicity, the efficiency and the easy accessibility of the reaction partners gives access to a wide array of heterocyclic frameworks equipped with a pendant pyridazinone unit. Various compounds of this group are presently under investigation.

Keywords: Pyridazinone, heterocyclic, physiologically active

1. Introduction

During the last few decades, much attention has been paid to the synthesis of pyridazin-3(2H)-one derivatives which possess important pharmacological activities. Depending on the type of substituted groups, derivatives of pyridazin-3(2H)-one show very different biological action: analgesic, anti-inflammatory, antibacterial, antivirus, antifungal, antitubercular, anti AIDs, antitumour, antihypertensive, anticonvulsant etc [1–10]. There are some drugs containing pyridazin-3(2H)-one moiety like Emorfazone (**Fig 1**) as analgesic and anti inflammatory [11], Sulmazole, SK&F-93741, Levosimendan, Amipizone, Indolidan, Y 590, Imazodan, Motapizone, Pimobedan etc (**figure 2**) as cardiotonic used in medical therapy [12-20]. Recently, much attention has been focused on pyridazine derivatives for their broad-spectrum activities. In addition, different pyridazinone derivatives are tested for various different biological activities for the treatment of various treatments.

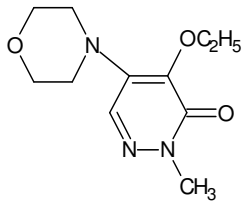

Fig.1 Emorfazone

2. Experimental

All chemicals were purchased from CDH (Central drug House) or Merck Co and used without purification. Melting points of the title compounds were recorded in open capillary tube in liquid paraffin bath and are uncorrected. Percentage yields were recorded. Solvent system used throughout the experimental work for running TLC plates was toluene, ethyl acetate and formic acid (TEF) in the ratio of 5:4:1. IR spectra were recorded by using KBr pellet technique on Perkin Elmer 337 IR spectrophotometer. ^{1}HNMR spectra were recorded in deuterated chloroform using tetra methyl silane (TMS) as an internal reference standard on BRUKER AVANCE II 400 NMR spectrometer.

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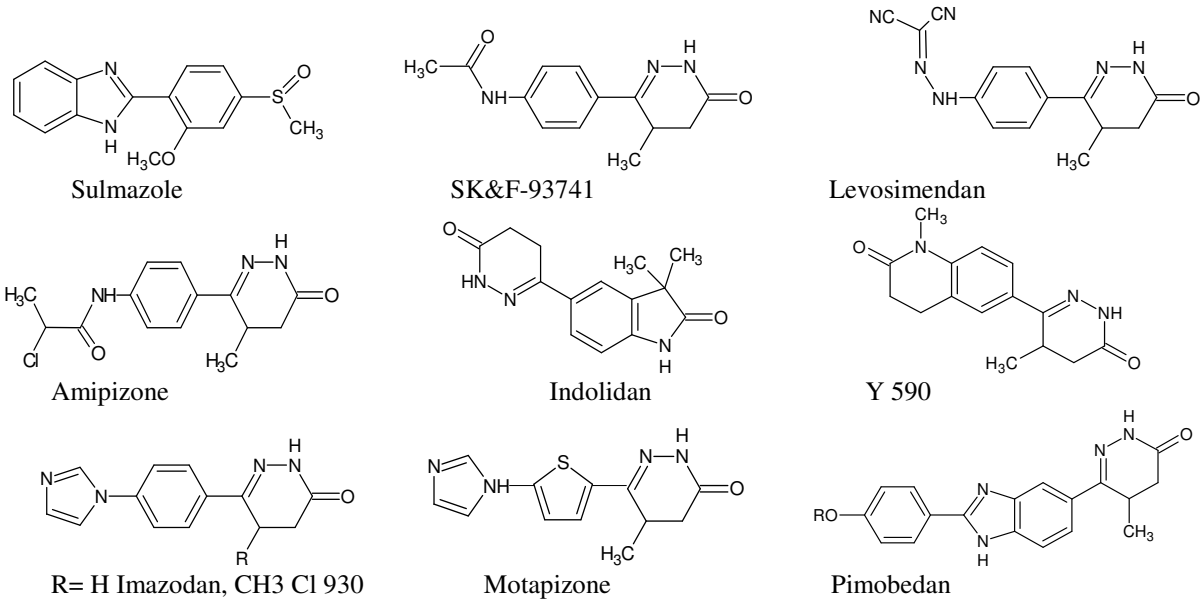

Fig.2. Various pyridazinone effective on cardio vascular system

In continuation to our work as such derivatives, the title compound was synthesized as shown in **Fig. 3** by following sequence of reactions: (I) Friedel crafts acylation of benzene with succinic anhydride in the presence of anhydrous aluminium chloride yielded β-benzoyl propionic acid, (II) Cyclization of β-benzoyl propionic acid to react with hydrazine hydrate to form 6-phenyl-2,3,4,5-tetrahydro pyridazin-3-one (pyridazinone ring), (III) Synthesis of 1-(3-bromopropyl)-1*H*-indole with 1,2-dibromoethane and indole in the presence of DMF (dimethylformamide) and anhydrous potassium carbonate, (IV) Synthesis of 2-[2-(1*H*-indol-1-yl)ethyl]-6-phenyl-4,5-dihydropyridazin-3(2*H*)-one with compound (**2**) and compound (**3**) in the presence of DMF (dimethylformamide) and anhydrous potassium carbonate.

3. Results and Discussions

1. Synthesis of β-benzoyl propionic acid:

After suspending anhydrous aluminum chloride (0.15 mol) in dry benzene (50 mL) under anhydrous conditions, the mixture was refluxed on a water bath. Succinic anhydride (0.10 mol) was then added to the reaction mixture in small portions with continuous stirring. Stirring and heating were continued for 6 h. The reaction mixture was left overnight at room temperature and then made acidic by addition of an ice cold solution of concentrated hydrochloric acid (2.5% v/v). The mixture was concentrated to a small volume by heating on a water bath. The separated precipitate was filtered. It was purified by dissolving in 5% w/v sodium bicarbonate solution, followed by extraction with ether. The aqueous layer on acidification with dilute hydrochloric acid gave benzoyl propionic acid. It was crystallized from aqueous ethanol to give a colorless compound.

M. P. 125^{0}C; yield 70%, Rf 0.25; IR Spectra: 3250 cm^{-1} (OH), 1720 cm^{-1} (C=O). 1H-NMR (δ, ppm): 2.59 (t, 2H, CH2), 3.23 (t, 2H, CH2), 7.53-7.62 (m, 3H, H-3'-H-5'), 7.97 (d, 2H, H-2' H-6'), 12.17 (s, 1H, COOH).

2. Synthesis of 6-phenyl-4,5-dihydropyridazin-3(2H)-one

To a solution of β-benzoyl propionic acid (**1**) (0.1 mol) in methanol (30 mL), hydrazine hydrate (1 mL) and sodium acetate (0.5 g) were added and the mixture was refluxed for 6 h.

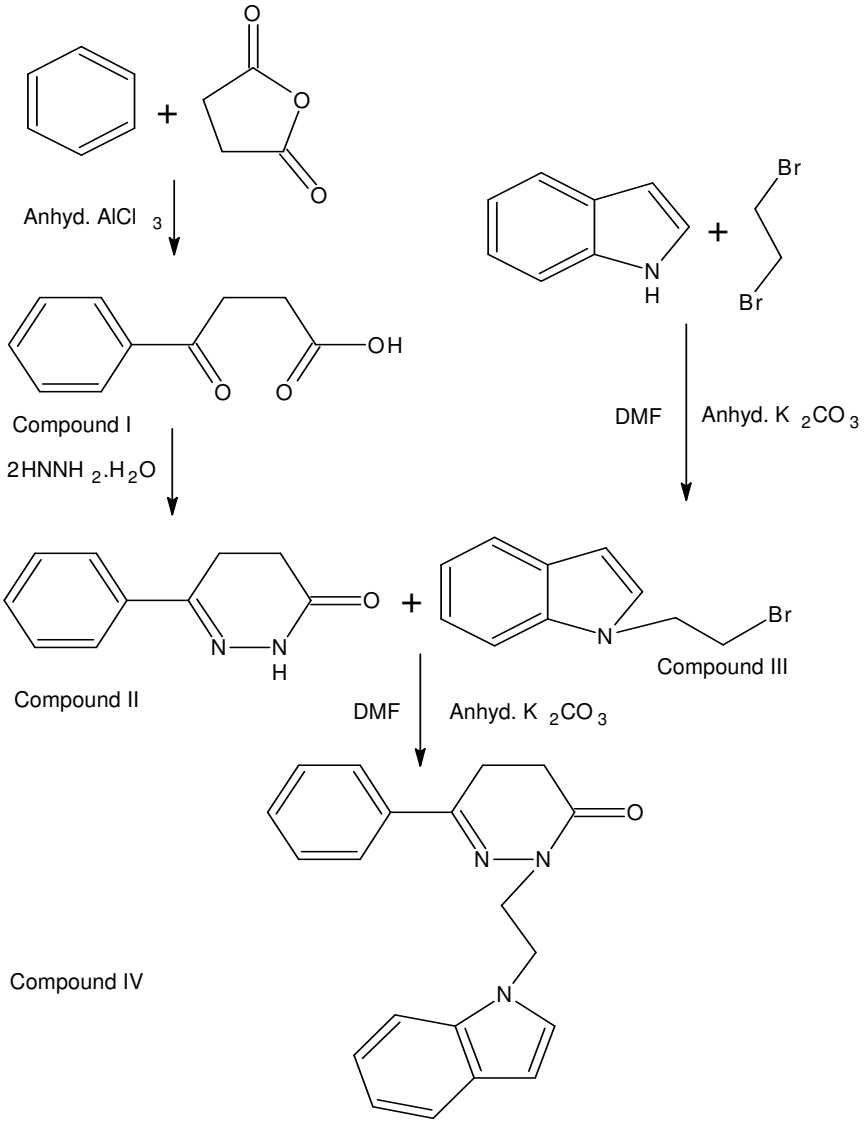

Fig.3. The secvence of reactions

After completion of the reaction, methanol was distilled off and the content was poured into cold water. The solid that separated out was filtered and crystallized from methanol.

M.P. 250 ^{0}C; Rf 0.45; 80% yield; IR (cm-1): 3306 (NH), 1678 (C=O); 3100cm^{-1} (CH).1H-NMR (δ, ppm): 2.45 (t,2H, CH2), 2.93 (t, 2H, CH2), 7.41(m, 3H, H-3'-H-5'), 7.74 (d, 2H, H-2', H-6'), 10.94 (s, 1H, CONH).

3. Synthesis of 1-(3-bromopropyl)-1H-indole

Indole (0.01 mol), potassium carbonate (0.04 mol) in 40 mL of dimethyl formamide and 1, 2-dibromo ethane (0.01 mol) was added, and stirred at 40□ C for 3hr . The reaction mixture was then poured into ice-water and the precipitate formed was filtered off, washed with water, dried and recrystallized from ethanol to obtain a yield of 80%.

4. Synthesis of 2-[2-(1H-indol-1-yl)ethyl]-6-phenyl-4,5-dihydropyridazin-3(2H)-one

Compound **2** (0.01 mol), potassium carbonate (0.04 mol) in 40 mL of dimethyl formamide and compound **3** (0.01 mol) was added, and stirred at 50 °C for 5hr . The reaction mixture was then poured into ice-water and the precipitate formed was filtered off, washed with water, dried and recrystallized from ethanol to obtain a yield of 60%.

M.P. 210 ^{0}C; yield 55%, IR (cm-1): 1700 (C=O); 3000cm^{-1} (CH). 1H-NMR (δ, ppm): , 2.03-2.08 (m, 4H, CH_2), 3.0 (t, 2H, CH2), 2.5 (t, 2H, CH2), 2.8 (d, 2H, CH_2), 2.3 (d, 2H, CH_2), 7.3(m, 3H, H-3'-H-5'), 7.74 (d, 2H, H-2', H-6').

4. Conclusions

The compounds were characterized on the basis of IR and ^{1}HNMR spectral data. IR spectrum showed the characteristics bond at 1700, 3450, and 1580 cm^{-1} authenticated the presence of C=O, NH and C=C groups. The ^{1}HNMR spectrum showed the signal in the form of multiplet near δ=2.8 for CH_2 protons at 5-position, another multiplet is observed at about δ=3.0 for CH_2 at 4 position. Aromatic proton also observed in the aromatic region ranging from δ=7.0-8.0. Presence of other substitutes also authenticated in the ^{1}HNMR spectra at the assigned value.

5. References

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