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Synthesis of Biologically Active N-Substituted 4-biphenyl Acetamide Derivatives

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A number of N-substituted (4-biphenyl)amides have been synthesized by condensation of 4-biphenyl acetic acid (4-BPAA) with $SOCl_2$ in dry benzene to prepare 4-biphenyl acetyl chloride. 4-Biphenyl acetyl chloride is then treated with different amides having one replaceable hydrogen ($–CONH_2$) to form new variety of amides (–CO–NH–CO–). The structure of newly synthesized compounds have been established by analytical and spectral methods.

Key Words: Synthesis, 4-Biphenyl acetic acid, N-Substituted 4-biphenyl acetamides.

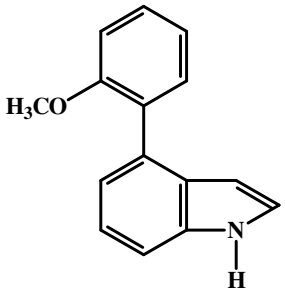
INTRODUCTION

Biphenyls are the polynuclear aromatic hydrocarbons (PAHS) having more than one aromatic nucleus. The two aromatic nuclei are attached to each other at only one point. Thus, biphenyls with independent benzene ring have been categorized in the class of polyphenyl compounds or isolated polynuclear hydrocarbons.

Biphenyl acetic acid and its derivatives have been found to be effective against many therapeutic diseases. Literature findings have also been shown its various therapeutic uses, *viz.*, antiinflammatory agent[1], as analgesic[2], antipyretic[3], antiarthritis[4], antirheumatoid[5], antihypertensive[2], a binder to human blood plasmapreal-bumen, *etc*.

4-Biphenyl acetic acid itself has been reported to possess many effective pharmacological activities, such as antiinflammatory, analgesic, antibacterial[6], and topical steroidal antiinflammatory activity[7]. The ointment and various types of patches containing 4-biphenyl acetic acid work very effectively as antiinflammatory and analgesic agents[8]. 4-Biphenyl acetic acid cyclodextrin inclusion compounds are reported to show effective mono-nuclear-rogenic antiinflammatory properties and its phenyl alkanamide derivatives have shown agro horticultural bacteriocidal activity[9]. Substituted biphenyls can also be used as antiallergic drugs[10].

Biphenyl compounds have stronger analgesic activity along with anti-allergic and antiinflammatory activity[6]. Substituted biphenyl 4 acetamide have therapeutic use in the treatment of cancer[11]. N-Substituted 4-biphenyl acetic acid used as an antitumor agent[12].



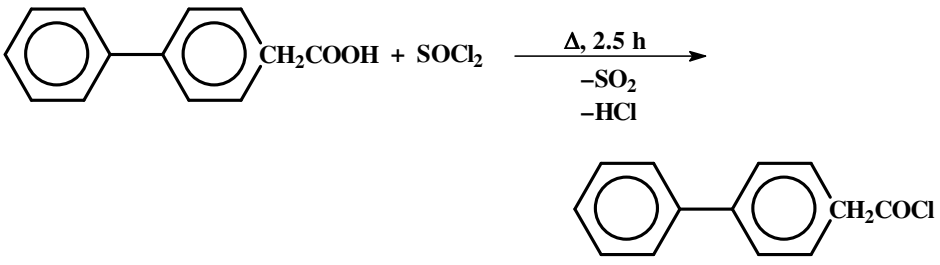
Structure of N-substituted 4-biphenyl acetic acid

Felbinac (an active metabolic of 4-BPAA) patch shows antiinflammatory and analgesic activities and also used in the treatment of adjuvant-arthritis[2]. Biphenyl-3-acetamide, 2-amino-thiazole shows anti-tumor activity also used in the treatment of cancer, alzheimer's disease, viral infections, auto-immune disease or neurodegenerative disorders[13].

2-Biphenyl acetic acid and 2-biphenyl acetamide used as agrochemical antifungal agents[14]. In view of these observations, it was proposed to synthesize N-substituted (biphenyl) amide derived from the condensation of 4-biphenyl acetic acid (4-BPAA) precursor and different amides having free ($-CONH_2$) group.

EXPERIMENTAL

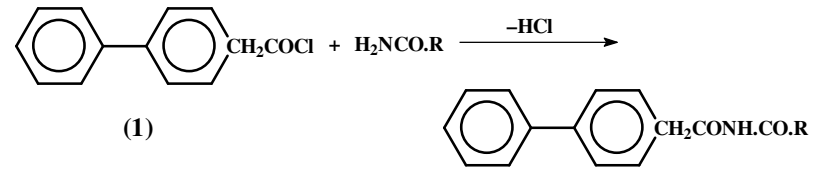
Synthesis of derived compounds (2 to 8) involves two steps: Preparation of 4-biphenyl acetyl chloride (1A) from 4-biphenyl acetic acid.



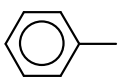
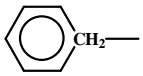
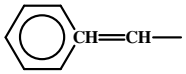
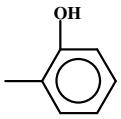
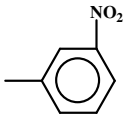
(1)

General procedure for the preparation of compound (1): Dissolved 4-biphenyl acetic acid (500 mg) in dry benzene (10 mL) in a round bottom flask of (50 mL) and added thionyl chloride (1 mL). Refluxed the reaction mixture for 2.5 h on water bath at 80 ºC. After 1 h the colour of reaction mixture change from yellow to orange. Concentrate the reaction mixture by recovering the benzene. 4-Biphenyl acetyl chloride obtained as a brown viscous oily substance, which (542 mg, 100 % yield) has used without further purification in next step to form various amides.

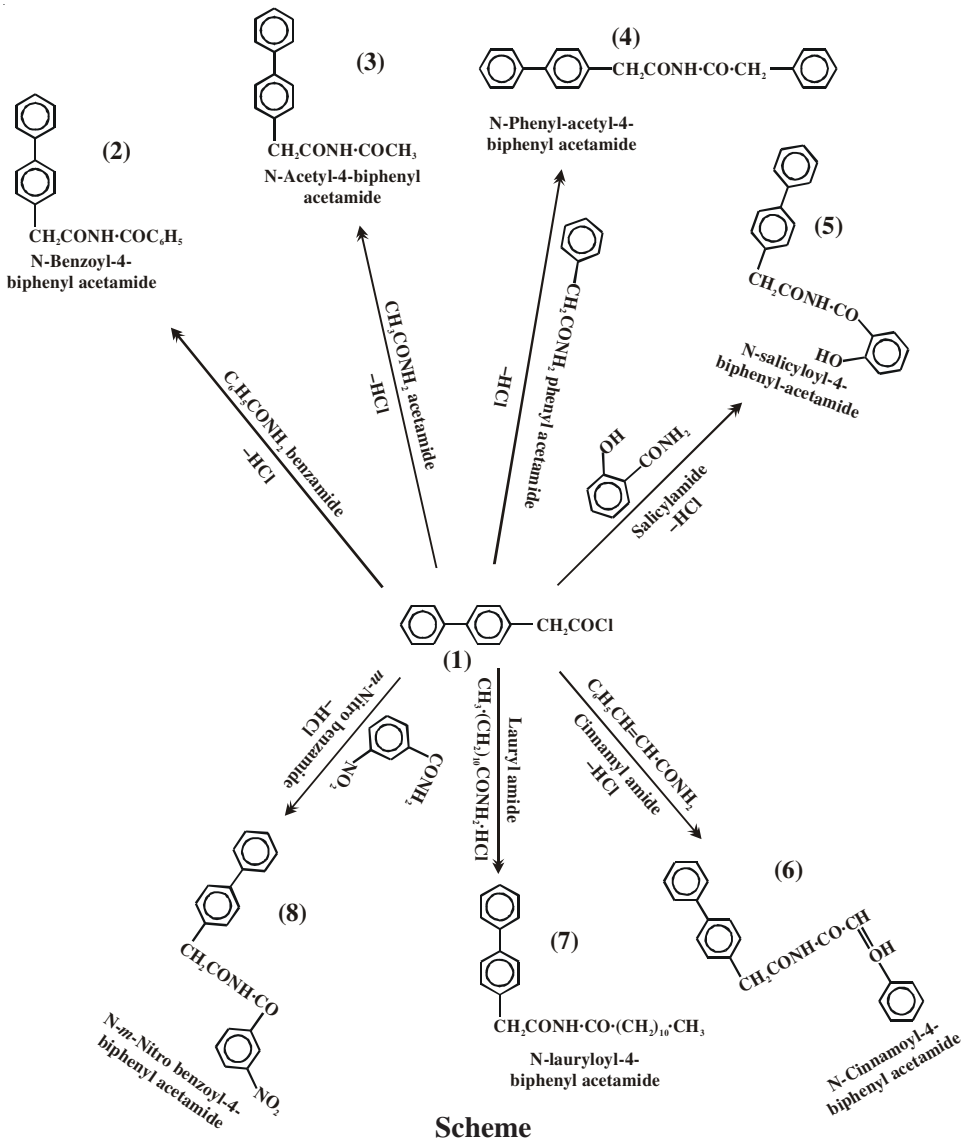
Preparation of N-substituted-4-biphenyl-acetamide from (1).



(1) **(2-8)**

Code of compound	Where		
2	R	=	
3	R	=	$-CH_3$
4	R	=	
5	R	=	
6	R	=	
7	R	=	$-(CH_2)_{10}CH_3$
8	R	=	

General procedure is described for the preparation of compounds (2-8): Dissolved the amide which has free $-CONH_2$ group in calculated amount in pyridine, now at this mixture in to round bottom flask containing (1), add dry benzene slowly drop by drop under stirring at room temp. Stirring continue for 3 h then check the TLC of reaction mixture shows that the reaction becomes complete, stirring continue upto the completion of the reaction and then work up the reaction mixture with suitable solvent after about 20 h reaction mixture. Reaction mixture takes in saperatory-funnel along with distilled water. Compound dissolved in the solvent, wash with water about 3-4 times to remove the basic nature of the solvent layer. The solvent layer becomes neutral, solvent layer was taken in conical flask and add $MgSO_4$ (to absorb the moisture of solvent layer), wait for 5-10 min. Filtered the solution in round bottom flask and recovered the solvent from reaction mixture by distillation and traces of solvent with the help of vacuum pump. Concentrate residue was treated with *n*-hexane for complete precipitation. Coloured crystalline solids obtained, filtered through Whattman filter paper (42), wash the precipitate with *n*-hexane about 3-4 times to remove coloured impurities of solid compound, dry and weigh.



Scheme

Characterizatioin of compounds

N-Benzyl 4-biphenyl acetamide (2): Pale yellow crystalline solid; m.p.: 128-130 ºC; yield: 0.26 g (43.96 %); TLC: R_f-0-482 (10 % MeOH: benzene); Elemental analysis: C=80.08 %, H=5.44 %, N=4.16 %; ^{1}H NMR (DMSO-d_6): δ 8.04 (14H-C_6H_5), δ 6.89 (1H-NH), δ 1.18 (2H-alicyclic CH_2).

N-Acetyl-4-biphenyl acetamide (3): White crystalline solid; m.p.: 118-119 ºC; yield: 0.27 g (49.09 %); TLC: R_f-0.470 (10 % MeOH: benzene); Elemental analysis: C=75.91 %, H=5.56 %, N=5.39 %, ^{1}H NMR (DMSO-d_6): δ 7.29 (9H-C_6H_5), δ 7.24 (1H-NH), δ 1.25 (2H-alicyclic CH_2) δ 2.38 (3H-alicyclic CH_3).

N-Phenyl acetyl-4-biphenyl acetamide (4): Mustard crystalline solid; m.p.: 133-135 ºC; Yield: 0.20 g (29.20 %); TLC: R_f-0.580 (5 % MeOH; $CHCl_3$); Elemental analysis: C=80.62 %, H=5.37 %, N=4.08 %; ^{1}H NMR DMSO-d_6: δ 8.02 (14H-C_6H_5), δ 7.42 (1H-NH), δ 1.09 (4H-alicyclic CH_2).

N-Cinnamoyl-4-biphenyl acetamide (5): Light pink crystalline solid; m.p.: 138-140 ºC; Yield: 0.35 g (46.62 %); TLC: R_f-0.607 (5 % MeOH: $CHCl_3$); Elemental analysis: C=80.75 %, H=5.38 %, N=4.06 %; ^{1}H NMR (DMSO-d_6): δ 7.98 (14H-C_6H_5), δ 7.56 (1H-NH), δ 1.17 (2H-alicyclic CH_2), δ 5.59 (2H-CH=CH).

N-Salicyloyl-4-biphenyl acetamide (6): Pale yellow crystalline solid; m.p.: 134-136 ºC; Yield: 0.36 g (50 %); TLC: R_f-0.540 (10 % MeOH: $CHCl_3$); Elemental analysis: C=76.23 %, H=5.05 %, N=4.31 %; ^{1}H NMR (DMSO-d_6): δ 7.82 (13H-C_6H_5), δ 7.49 (1H-NH), δ 3.65 (1H-OH), δ 1.21 (2H-alicyclic CH_2).

N-Lauryloyl-4-biphenyl acetamide (7): White crystalline solid; m.p.: 148-150 ºC; Yield: 0.33 g (39.70 %); TLC: R_f-0.540 (10 % MeOH: $CHCl_3$); Elemental analysis: C=81.64 %, H=6.41 %, N=3.63 %; ^{1}H NMR (DMSO-d_6): δ 7.68 (9H-C_6H_5), δ 6.71 (1H-NH), δ 1.12 (22H-alicyclic-CH_2), δ 2.21 (3H-alicyclic CH_3).

N-Metanitrobenzoyl-4-biphenyl acetamide (8): Mustard crystalline solid; m.p.: 132-134 ºC; Yield: 0.68 g (90.42 %); TLC: R_f-0.621 (10 % MeOH: $CHCl_3$); Elemental analysis: C=70.36 %, H=4.49 %, N=8.10 %; H^{1}NMR (DMSO-d_6): δ 7.79 (13H-C_6H_5), δ 6.67 (1H-NH), δ 1.29 (2H-alicyclic-CH_2).

RESULTS AND DISCUSSION

Commercially available 4-biphenyl acetic acid was used for the preparation of such types of amides having [–CO–NH–CO–] type bonding. First of all 4-biphenyl acetic acid is treated with $SOCl_2$ in dry benzene on water bath for 2-3 h. After 1 h the colour of reaction mixture becomes change from pale yellow to orange and then on completion of reaction it changes from orange to brown.

This oily mass of 4-biphenyl acetyl chloride is then treated with different types of amides having free $–NH_2$ group. These amides are however commercially available but we synthesized most of these amide by treating particular acid with $SOCl_2$ in dry benzene to prepare particular acetyl chloride and then acetyl chlorides treated with ammonia in pyridine.

Simple prepared amides were then treated with 4-biphenyl acetyl chloride to prepare different types of amides having [–CO–NH–CO–] type bonding. Prepared amides are treated with *n*-hexane for crystallisation. Pure compounds are then analysed by measured m.p., TLC, elemental analysis, NMR, *etc*.

Biological activities: All 4-biphenyl amides have been studied for their antifungal activity against *Fujenum udum* and *Curvalaria lunata*. The culture of each species was incubated at 12 ± 3 ºC and the zone of the inhibition was measured after 120 h. Most of these compounds were found active against these cultures.

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