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Synthesis, characterization and anti inflammatory activity of 4{[(phenyl substituted) (2-methyl-3a, 7a-dihydro-1h-indol-1-yl) benzyl] amino} benzoic acid

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ABSTRACT

A variety of 4{[(phenyl substituted) (2-methyl-3a, 7a-dihydro-1H-indole-1-yl) benzyl] amino} benzoic acid (**IV** a-e) have been synthesized by reacting 2-phenyl indole(**III**) with Para amino benzoic acid with ethanol. The starting material 2-phenyl indole (**III**) was synthesized from phenyl hydrazine (**I**) with acetophenone(**II**). The title compounds obtained were characterized by IR, ^{1}H NMR and Mass spectral data. The prepared compounds were screened for their anti-inflammatory activity by carrageenan induced paw odema method in rats.

Keywords: 2-phenyl indole, Acetophenone, Anti inflammatory.

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INTRODUCTION

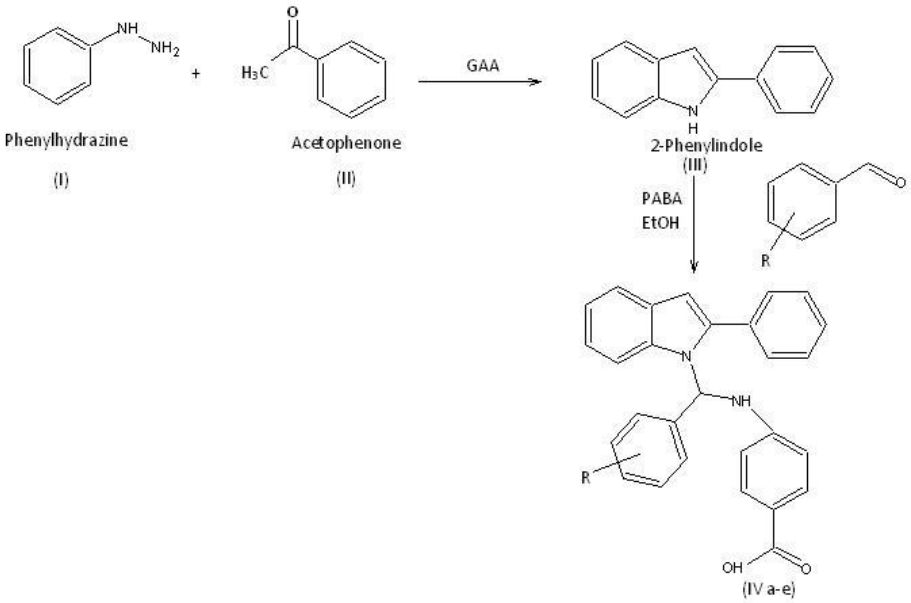
Heterocyclic play a vital role in pharmacological, agricultural and synthetic fields [1]. Consequently, the development of methodologies useful for the assembly of molecules containing heterocyclic templates continues to attract the attention of both the industrial and academic communities. In continuation of our efforts in search of bioactive molecules, a number of indole and furan derivatives have been synthesized using microwave irradiation and evaluated for anti inflammatory and analgesic activity [2]. The relative abundance of indole based therapeutics agents is attributable only in part to the fact that this nucleus forms part of a pharmacophore for selected CNS agents. The indole moiety likely serves as a rigid bicylcic support in case of majority of agents. The presence of acidic proton forms a recurring feature among the clinically successful NSAID'S.

MATERIALS AND METHODS

Experimental

Melting points were determined in open capillary tubes on a scientific melting point apparatus and are uncorrected. IR spectra were recorded in KBr on a JASCO FTIR 460 spectrometer. Mass spectra were taken on a BRUKER DPX (200 MHZ) spectrometer using TMS as internal standard. Elemental analysis was performed on SHIMADZU QP 50000.

Synthesis of 2-phenyl-3a, 7a dihydro-1H-indole (III)



a)R=H, b) R=2-OH, c) R=2,4-dichloro, d)R=2-chloro, e) R=3-methoxy,4-hydroxy

Scheme-1

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In a 500ml three necked flask fitted with a dropping funnel, a sealed stirred unit and reflux condenser placed a mixture of 0.1 mol of acetophenone (**II**) and 0.1 mol acetic acid heated under reflux with stirring and added 0.1 M of phenyl hydrazine **(I**) during in continued the stirring for another one hour. Poured the reaction mixture into a 1 liter beaker and stirred vigorously while it solidifies cooled to 5^0C and filtered at the vaccum pump through Buchner funnel, cooled the filtrate in ice and re filtered through the same Buchner funnel, washed the solid on the filter with 50ml of water, sucked almost dry and then washed with 50 ml of ethanol then kept overnight in room temperature, recrystallized from ethanol.

4{[(phenyl) (2-methyl-3a, 7a-dihydro-1H-indole-1-yl) benzyl] amino} benzoic acid (IV a)

A mixture of 2-phenyl-3a, 7a, dihydro-1H-indole (**III**) (1.89 g, 0.01mol) para amino benzoic acid (1.37 g, 0.01mol) and benzaldehyde (1.06 ml, 0.01mol) in ethanol (40 ml) were refluxed for 4 hr and excess of solvent was removed by distillation. The resulting solid was dried and recrystallized from dilute ethanol to brown crystals.

IV a: Yield 66.8%, M.P. of 94-96^0C was analyzed for $C_{28}H_{21}N_2O_2$. IR (KBr): 3277 (-NH-), 3060 (Ar-CH), 1724 (COOH), 1624 (Ar-C=C), 1584 (-C=C- attached to N), 1483 (C-N). The ^{1}H NMR:11.21(s,1H-NH), 9.68 (s, 1H, Ar-COOH), 7.47-8.42 (m, 8H, Ar-H), 7.47(d, 2H, Ar-H 5th and 6th proton of indole.),7.28 (d, 2h, Ar-H 4th and 7th proton of indole), 6.48 (s, 1H, H-3 of indole ring), 7.08 (d, 2H, Ar-H 2nd and 6th proton of N-Phenyl ring), 6.8 (d, 2H, Ar-H-3rd and 5th proton of N-Phenyl ring).

Synthesis of 4{[(2-hydroxy phenyl) (2-methyl-3a, 7a-dihydro-1H-indole-1-yl) benzyl] amino} benzoic acid (IV b)

A mixture of 2-phenyl-3a, 7a, dihydro-1H-indole (**III**) (1.89 g, 0.01mol), para amino benzoic acid (1.37 g, 0.01mol) and salicyaldehyde (1.12 ml, 0.01mol) in ethanol (40 ml) were refluxed for 4 hr and excess of solvent was removed by distillation. The resulting solid was dried and recrystallised from dilute ethanol to obtain light yellow crystals.

IV b: Yield 58.5%, M.P. of 140-142^0C was analyzed for $C_{28}H_{22}N_2O_3$. IR (KBr): 3366 (-NH-), 3495 (phenolic OH), 3095 (Ar-CH), 1732 (C=C attached to N), 1441 (-C-N). The ^{1}H NMR:11.22 (s, 1H, NH), 10.27 (s, 1H, phenolic OH), 9.26 (s,1H,Ar- COOH), 7.22 (d, 2H, Ar-H 4th and 7th proton of indole.),7.06(d, 2H, Ar-H 2nd and 6th proton of N-phenyl ring), 6.82(d, 2H, Ar-H 3rd and 5th proton of N-Phenyl ring),6.42(s, 1H, H-3 of indole). MS:m/z:434(M^+), 406, 199, 193 and 117.

Synthesis of 4{[(2, 4, dichloro phenyl) (2-methyl-3a, 7a-dihydro-1H-indole-1-yl) benzyl] amino} benzoic acid (IV c)

A mixture of 2-phenyl-3a,7a,dihydro-1H-indole (**III**) (1.89 g, 0.01mol) para amino benzoic acid (1.37 g, 0.01 mol) and 2,4 dichloro benzaldehyde (1.74 ml, 0.01mol) in ethanol (40

ml) were refluxed for 4 hr and excess of solvent was removed by distillation. The resulting solid was dried and recrystallized from glacial acetic acid to obtain brown crystals.

IV c: Yield 67%, M.P. of 120-122^{0}C was analyzed for $C_{28}H_{20}Cl_2N_2O_2$. IR (KBr): 3306 (-NH-), 3025 (Ar-CH),1699 (COOH), 1624 (Ar-C=C -), 1604 (-C=C attached to N), 1456 (C-N), 759 (C-Cl). The ^{1}H NMR:11.28 (s, 1H, NH), 9.67 (s, 1H, Ar-COOH), 7.47-8.47 (m, 8H, Ar-H), 7.92 (d, 2H, Ar-H 2nd and 6th proton of N-Phenyl ring), 6.82 (d, 2H, Ar-H 3rd and 5th proton of N-phenyl ring), 7.22 (d, 2H, Ar-H 5th proton and 6thproton of indole), 7.02 (d, 2H, Ar-H 4th proton and 7thproton of indole), 6.48 (s,1H H-3 of indole ring).

Synthesis of 4{[(2-chloro phenyl) (2-methyl-3a, 7a-dihydro-1H-indole-1-yl) benzyl] amino} benzoic acid (IV d)

A mixture of 2-phenyl-3a, 7a, dihydro-1H-indole **(III**) (1.89 g, 0.01mol) para amino benzoic acid (1.37 g, 0.01mol) and 2-chloro benzaldehyde (1.40 ml, 0.01mol) in ethanol (40 ml) were refluxed for 4 hr and excess of solvent was removed by distillation. The resulting solid was dried and recrystallised from dilute ethanol to obtain brown crystals.

IV d: Yield 68%, M.P. of 130-132^{0}C was analyzed for $C_{28}H_{21}Cl_2N_2O_2$. IR (KBr): 3286 (-NH-), 3010 (Ar-CH), 1734 (COOH), 1604 (Ar-C=C -), 1596 (C=C attached to N),1422 (C-N), 752(C-Cl).The ^{1}H NMR:11.20 (s, 1H, NH), 9.68 (s, 1H, Ar-COOH), 7.47-8.42 (m, 8H, Ar-H), 7.28 (d, 2H, Ar-H 5th and 6thproton of indole) , 7.08 (d, 2H, Ar-H 4th and 7thproton of indole), 7.97 (d, 2H, Ar-H 2nd and 6thproton of N-phenyl ring), 6.82 (d, 2H, Ar-H 3rd and 5thproton of N-phenyl ring), 6.48 (s, 1H, H-3 of indole ring).

Synthesis of 4{[(4-hydroxy, 3-methoxy phenyl) (2-methyl-3a, 7a-dihydro-1H-indole-1-yl) benzyl] amino} benzoic acid (IV e)

A mixture of (2-phenyl-3a, 7a, dihydro-1H-indole (**III**) (1.89 g, 0.01mol) para amino benzoic acid (1.37 g, 0.01mol) and vanillin (1.52g, 0.01mol) in ethanol (40 ml) were refluxed for 4 hr and excess of solvent was removed by distillation. The resulting solid was dried and recrystallised from dilute glacial acetic acid to obtain light brown crystals.
IV e: Yield 67%, M.P. of 160-162^{0}C was analyzed for $C_{29}H_{24}N_2O_4$. IR (KBr): 3366 (-NH-), 3495 (phenolic OH), 3095 (Ar-CH), 1732 (C=C attached to N), 1441 (C-N). The ^{1}H NMR:11.21 (s, 1H, NH), 10.24 (s,1H, OH),9.62(s,1H,Ar-COOH), 7.22 (d, 2H, Ar-H 4th and 7thproton of Indole) 7.62-8.42 (m, 9H, Ar-H), 7.47(d, 2H, Ar-H 5th and 6thproton of Indole) , 7.06 (d, 2H, Ar-H 2nd and 6thproton of N-phenyl ring), 6.82 (d, 2H, Ar-H 3rd and 5thproton of N-phenyl ring), 6.42 (s, 1H, H-3 of indole).

The synthesized derivatives were evaluated for in vivo anti-inflammatory assay methods

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Anti inflammatory activity

Carrageenan-induced paw edema in rats

The title compounds (**IV** a-e) were screened for anti inflammatory activity[3-6].The anti inflammatory activity was carried out by rat paw odema method[7]. Male albino rats of 12 groups (6 no's in each) were taken for study. Group one was kept control, group two was treated with standard drug Ibuprofen 20mg/kg body weight and the remaining groups were administered with test compounds also in the same concentration. A mark was made on left paws just beyond tibio-tarsal junction(knee joint) of each animal of all groups, so that each time the paw edema meter(520-R, IITC Life science, USA) up to the fixed mark made on left paws to ensure constant paw volume. Carrageenan(1%, 0.1mL)was injected subcutaneously into the plantar surface of the rat hind paw 1hr after the oral administration of the test compound. After the administration of carrageenan solution, the paw volume of control, standard and test groups were noted at 1hr, 2hr, 3hr and 4hr time interval. The percentage of inhibition was calculated by applying New bould formula[8].

CONCLUSION

% inhibition in paw thickness at various time intervals

Compound code	After 1 hr	After 2 hr	After 3 hr	After 4 hr
Control	0.97±0.016	93±0.017	0.91± 0.013	0.89± 0.01
Ibuprofen	0.61±0.008 37.11	0.53±0.011 42.85	0.41±0.008 54.5	0.30±0.003 **65.74**
IV a	0.65±0.006 33.21	0.56±0.008 39.35	0.51±0.004 44.01	0.31±0.004 **64.99**
Iv b	0.73±0.010 26	0.66±0.011 28.57	0.53±0.005 45.25	0.50±0.006 44.41
IV c	0.88±009 10.06	0.55±0.005 40.35	0.46±0.007 49.08	0.40±0.004 54.81
IV d	0.88±0.009 9.19	0.68±0.008 39.28	0.50±0.023 44.01	0.42±0.003 52.29
IV e	0.75±0.009 23.33	0.56±0.015 28.57	0.46±0.003 49.08	0.38±0.003 **57.44**

All values are expressed as Mean±SEM

The pharmacophore 4{[(phenyl substituted) (2-methyl-3a, 7a-dihydro-1H-indole-1-yl) benzyl] amino} benzoic acid exhibited anti inflammatory activity with different subtituent in different percentages. Compound (**IV** a) exhibited 64.99 % and compound (**IV** e) exhibited 57.44% anti inflammatory activity when compared to the standard drug Ibuprofen which showed 65.74% activity. The remaining compounds showed mild moderate (44.41-54.81%) activity. So it confirms that the above mentioned compound having excellent anti inflammatory activity.

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REFERENCES

[1] Lang SA & Lin Yi, in comphrehensive Heterocyclic chemistry, edited by AR Katritzky & C W Rees (Pergamon press, Oxford). 1984; 6: 1.
[2] NA Begum, N Roy, S Mandal, S Basu and D Mandal. J Luminescence 2009; 129: 158.
[3] Szmuszkovicz J, Glenn EM, Heinzelamn, RV Hester, JB, Youngdale GA. J Med chem 1966; 91: 527.
[4] Sreenivasulu N, Sonar VN, Yazadan SK. Indian J Het Chem2001; 10: 299-302.
[5] SK Srivastava, S Srivastava & SD Srivastavo. Indian J Het Chem Sec B 1999; 38 B: 183-187.
[6] A Rajasekaran, R Mahesh and ZK Khan. Indian J Het Chem 1998; 8: 151-152.
[7] RA Turner "Screening Methods in Pharmacology", Satya Publishers, Madurai 1965; 100.
[8] Newbould BB. Brit J Pharmacology.1963; 21: 127.