SYNTHESIS AND ANTIDEPRESSANT ACTIVITY OF TETRAHYDRO BENZOTHIOPHENE DERIVATIVES.

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Abstracts : The synthesis, structure and biological activity of benzothiophene has been long focus of research interests in the field of Medicinal Chemistry. Benzothiophene nucleus has been established as the potential entity in the largely growing chemical world of heterocyclic compounds possessing promising pharmacological characteristics. A series of tetrahydro benzothiophene derivatives were synthesized with an objective to develop novel and potent antimicrobial agents of synthetic origin. The required starting material 2-amino-4,5,6,7-tetrahydro-1-benzothiophene-3-carboxylate(1) was synthesized via a multicomponent condensation between sulphur, cyclohexanone and ethylcyanoacetate adopting Gewald Reaction.The Compound 2-amino-4,5,6,7-tetrahydro-1-benzothiophene-3-carboxylate (1) was converted to respective substituted chloroacetanilide (2). The synthesized compound were further processed into the final compounds i.e.2-{[Substituted-phenylcarbamoyl)-methyl]-amino}-4,5,6,7-tetrahydro-benzo[b]thiophene-3-carboxylic acid ethyl esters. All synthesized compound were characterized by IR, H1-NMR and elemental Analysis. All the newly synthesized derivatives were screened for Antidepressant activity using Sertraline HCL as a standard.[1]

Key Words: Tetrahydrobenzothiophenes, Antidepressant.

Introduction : Benzothiophene have been shown to have a broad range of important biological activities including antibacterial, antimicrobial, analgesics, anti-inflammatory, antifungal,Antidepressant etc. In order to synthesize active molecule of widely different composition such as combination of two heterocyclic frameworks to achieve good biological profile. It was planned to synthesize some benzothiophene derivative.[1] The synthesis of 2-amino-3-carbethoxy-4,5,6,7-tetrahydro benzothiophene was performed following steps shown in reaction scheme I. The required compound 1 has been prepared by reaction of cyclohexanone with ethylcyanoacetate using diethylamine by stirring the mixture for 30 min. The compound II substituted chloroacetanilide(2a-h) was synthesized and Equimolar quantities of 2-amino-3-carbethoxy-4,5,6,7-tetrahydro benzothiophene and substituted chloroacetanilide was dissolved in dry 1,4 dioxane to this triethylamine was added reaction mixture was refluxed for 2hr it was Monitored by Tlc cooled, poured onto crushed ice solid. Precipitate was filtered dried and. Recrystallized from ethanol. Gives compound 2- {[(Substituted phenylcarbamoyl)-methyl] -amino}-4,5,6,7-tetrahydro-benzo[b]thiophene-3-carboxylic acid ethyl ester (3a-h) The homogeneity of all the synthesized compound was checked by TLC. The structures of synthesized compounds were assigned on basis of spectral data like IR, H1-NMR spectral analysis. All the synthesized compounds were screened for biological activities like analgesic and invitro anti-inflammatory activities Antidepressant.[2,3]

Materials and Methods In this research work, the melting points of synthesized compounds were determined by open capillary tubes using paraffin bath and are uncorrected. Thin layer chromatography is among the most useful tools for following the progress of organic chemical

reactions and for assaying the purity of organic compounds. To prepare TLC, clean and dry glass plates were taken. Uniform slurry of silica gel-G in water was prepared in ratio of 1:2. The plates were prepared manually by spread plate method. These were dried first at room temperature and then kept for activation at 110°C for 1 hour. However, Acetone: Benzene having proportion (1:1) was found suitable for most of the synthesized compounds. IR spectra were recorded on a JASCO FT-IR 4100 spectrophotometer, using KBr powder technique. The NMR spectra of the compounds were recorded on a Varian-NMR-mercury 300 MHz spectrophotometer from Pune University, in CDCl3 using TMS as an internal standard. [3]

Biological Investigation: The synthesized compounds were evaluated for Antidepressant activities. The standard and test compounds were administered i.p. and orally. The statistical analysis was done by using One way ANOVA followed by Dunnet test.

Antidepressant activity : Male albino mice of weight range 20-25 gm were selected for study. They were grouped in different comprising of 6 animals in each group. Before study food was withdrawn but animal had free access to water. Test compounds were administered orally at a dose of 100 mg/ kg body weight suspended in sterile water for injection. Standard group received sertraline HCL at a dose of 20 mg/kg body weight Orally. Turn on the Actophotometer (check and make sure that all the photocells are working for accurate recording) and place individually each mouse in the activity cage for 10 min. Note the basal activity score of all the animals. Inject Sertraline HCl 20 mg/kg body weight and after 30 min re-test each mouse for activity score for 10 min. Note the difference in the activity before and after administration of Sertraline HCl. Calculate percent decrease in motor activity. The results are presented in Table 2. [4]

Antidepressant activity : Statistical analysis was performed by one-way ANOVA followed by Dunnett's test. n = 6; dose = 100 mg/kg. Values are represented as mean ± S.E.M. Values are significant at ***P < 0.001, compared with control group. ns: not significant (P < 0.05) as compared to vehicle-treated group.Percentage decrease in immobility duration (%DID) for test and standard drugs was calculated using following formula:

$$\%DID = \left[\frac{A-B}{A}\right] * 100,$$

Experimental

Route of synthesis

Step I: Synthesis of 2-amino-3-carbethoxy-4,5,6,7-tetrahydro benzothiophene (1): Synthesis of 2-amino-3-carbethoxy-4,5,6,7-tetrahydro benzothiophene (1) was carried out by mixing cyclohexanone (0.2 mol), ethylcyanoacetate (0.2 mol) and sulphur (0.2) in ethanol (40 ml), and diethylamine (0.2 mol) was added drop wise with stirring. Yellow colored crystals were obtained which was collected, dried and recyrstallized with ethanol.[5]

StepII : Synthesis of Substituted chloroacetanilide (2a-h) : Substituted aniline (0.1 mole) were dissolved in glacial acetic acid and saturated solution of sodium acetate.To this chloroacetyl chloride (0.12 mole) was added drop wise with stirring.After Half an hour white precipitate was obtained,it was filtered,dried and recrystalized from ethanol. [6]

Step III: Synthesis of 2- {[Substituted-phenylcarbamoyl) - methyl]-amino}- 4,5,6,7-tetrahydro-benzo[b]thiophene-3-carboxylic acid ethyl ester (3a-h)

Equimolar quantities of 2-amino-3-carbethoxy-4,5,6,7-tetrahydro benzothiophene and subsitituted chloroacetanilide was dissolved in dry 1,4 dioxone to this triethylamine was added reaction mixture was refluxed for 2hr it was then cooled,poured onto crushed ice solid. precipitate was filtered dried and. Recrystallized from ethanol[7]

5.1.1: -amino-3-carbethoxy- 4,5,6,7-tetrahydro benzothiophene derivatives.(4a)

IR Vmax (cm-1), 3298cm-1 –NH2, 3169cm-1 Ar-CH,1180cm-1 –CN, 1572,–C=O,977,896cm-1–C=C-S, 1597.71-C=C

,638,781N-H.

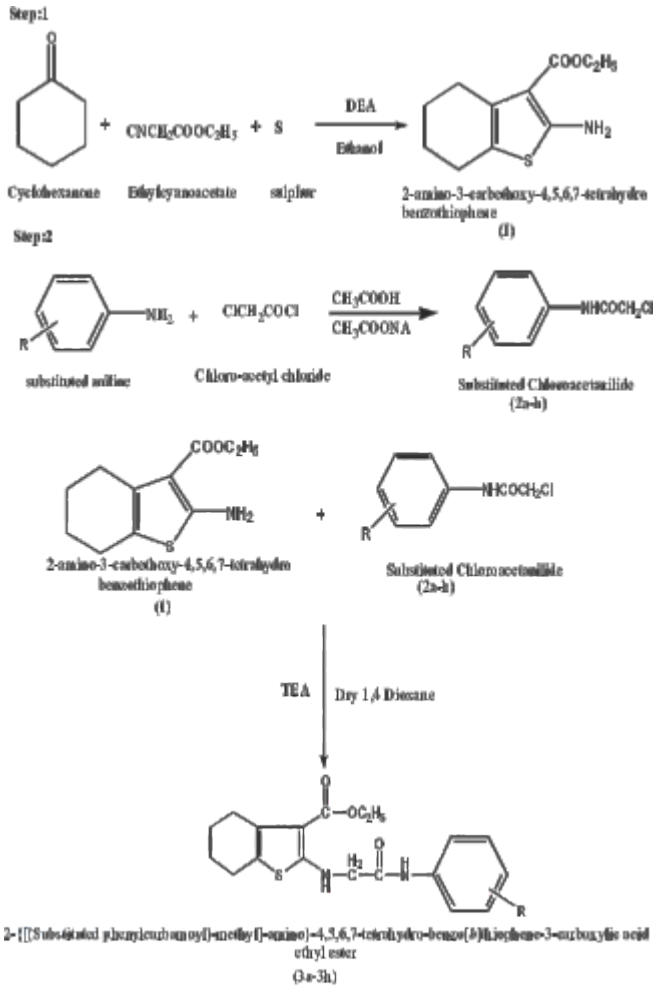
5.1.2:-{[(3-Nitro-phenylcarbamoyl)-methyl]-amino}-4,5,6,7-tetrahydro-benzo[b]thiophene-3-carboxylic acid ethyl ester : IR Vmax (cm-1), 1603.13cm-1–N-H, 1253cm-1 -C-H, 1147.72cm-1 C-N, 2190.69cm-1 N=O, 1746.12 cm-1 –C=O, 1355cm-1 –CN, 1494.32cm-1C=C, 690.60cm-1C-S. 1255.54cm-1 C-O,

5.1.3:2-{[(3-Bromo-phenylcarbamoyl)-methyl]-amino}-4,5,6,7-tetrahydro-benzo[b]thiophene-3-carboxylic acid ethyl ester : IR Vmax (cm-1), 1110.93cm-1 C-N, 1659.03cm-1–N-H, 1269.29cm-1 C-H , 659.12cm-1 C-S, 1746.12 cm-1 –C=O, 1260cm-1 C-N, 1446.79cm-1–C=C, 659.12 cm-1-Br, 1210.76 cm-1 -C-O ,1H NMR (300MHz) (CDCl3), d (ppm) 7.8 (t, 8H, Aryl), 4.1- 4.2 (m, 5H, COOC2H5), 1.6(d, 8H, CH2),

Result and Discussion

Pharmacological Screening : All the synthesized compounds were subjected to antideprresent activity at a 200 mg/kg; body weight dose using sertraline HCl as a Standard. All the synthesized compounds showed significant Antidepressant activity as compared to the standard sertraline HCL. The synthesized compounds have different concentration, the absorbance was measured and calculated the percentage inhibition and IC50 value. The results for evaluation of Antidepressant activity are presented in table 2 respectively. Compounds 3e, and 3h exhibited excellent antideprresent activity .

Conclusion : Substituted benzothiophene derivative was synthesized and to screen the synthesized compounds for antideprresent activity. The compounds planned for synthesis were prepared under available laboratory conditions and purity of the compounds were checked by melting point and Rf value and structural confirmation is done by IR and 1HNMR data. Amongst all synthesized compounds 3e, And 3h exhibited significant antideprresent activity as compared to standard and the standard drug sertraline HCL.



Scheme : 1 Table no 1: Physical data of synthesized compounds

Comp. no.	R	Molecular Formula	Mol. Wt. (gm)	Melting point (0C)	% yield	Rf values
3a	$3NO_2$	$C_{19}H_{27}N_3O_5S$	409	112-115	73%	0.86
3b	4Br	$C_{19}H_{27}BrN_2O_3S$	433	124-127	78%	0.70
3c	4cl	$C_{19}H_{27}ClN_2O_3S$	398	103-106	86%	0.77
3d	$4NO_2$	$C_{19}H_{27}N_3O_5S$	409	134-137	67%	0.81
3e	3-Cl	$C_{19}H_{27}ClN_2O_3H$	400	138-140	70%	0.85
3f	$2\text{-}NO_2$	$C_{19}H_{27}N_3O_5S$	409	141-145	75%	0.80
3g	3-Br	$C_{10}H_{27}BrN_2O_3S$	443	150-155	65%	0.75
3h	aniline	$C_{19}H_{29}N_30_3S$	339	184-188	75%	0.78

Table 2: Antidepressant activity data of 2-{[(Substituted-phenylcarbamoyl)-methyl]-amino}-4, 5, 6,7-tetrahydro-benzo[b]thiophene-3-carboxylic acid ethyl ester.(3a-h)

Group	Compound	Dose (mg)	Duration of immobility in (sec)	% DID	Locomotor activity for 10min (sec) mean ± S.E.M
I	Control	–		0.0	390 ± 15
II	Standard	20 mg	20.3 ± 0.6***	73.7	370 ± 14ns
III	3a	100 mg	33.2 ±3.9***	59.4	350 ± 16.0ns
IV	3b	100 mg	54.7 ± 2.1***	37.0	370 ± 9.0ns
V	3c	100 mg	23.1 ± 2.6***	70.5	360 ± 17.0ns
VI	3d	100 mg	20.7 ± 1.4***	73.1	360 ±13.0ns
VII	3e	100 mg	12.8 ± 0.3***	86.0	340 ±13.0ns
VIII	3f	100 mg	38.2 ± 3.9***	55.4	330 ± 14.0ns
IX	3g	100 mg	47.4 ± 4.5***	45.6	320 ± 29.0ns
X	3h	100 mg	26.5 ± 1.2***	79.2	290 ± 28.0ns

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