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Research Article

SYNTHESIS, CHARACTERIZATION AND CNS DEPRESSANT ACTIVITY OF SOME SCHIFF BASES OF 2-AMINO-N-(O-FLUOROPHENYLCARBOXAMIDO)-4-(P-METHOXYPHENYL) THIOPHENES

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ABSTRACT

The novel 2-amino-N-(o-fluorophenylcarboxamido)-4-(p-methoxyphenyl)-thiophene [I] was synthesized by using a pioneer method and the parent compound [I] was reacted with different substituted aryl aldehydes to obtain a series of title compounds [I a-l]. All the new title compounds were characterized by spectral data and were screened for CNS depressant activity.

In conclusion, it can be inferred that the electron donating groups on the phenyl ring at R of the title compounds influenced the CNS depressant activity.

Keywords: Synthesis, Thiophene, Schiff Base, Characterization, CNS Depressant activity

INTRODUCTION

In medicinal chemistry thiophene derivatives have been very well known for their therapeutic applications. The benzo[b]thiophene system often present in biologically active compounds and many examples of biological activities found for small nucleus based on the benzo[b]thiophene moiety can be referred. The literature indicated that compounds having benzo[b]thiophene nucleus possess broad range of biological activities namely anti-inflammatory[1],antifungal[2], analgesic[3], antitumor[4], alkaline phosphatise inhibitor[5] and antimicrobial[6] activities.

Schiff Bases attract much interest both for synthetic and biological point of view[7]. Thus, they can be used in the preparation of pharmaceuticals, plastics, as well as pesticides and can occur as intermediates in much enzymatic reaction. Schiff base exhibit powerful anti-inflammatory, analgesic, ulcerogenic[8] antibacterial, antifungal, anti-HIV[9], antimicrobial[10], anticonvulsant[11] activities. Meanwhile, useful pharmacological properties are also associated with presence of 5- and 6-membered heterocyclic rings in drug molecules. This prompted us to design and prepare new 2-amino benzo[b]thiophene by adaptation of well known and versatile Gewald reaction[12] and their Schiff bases where in two moieties incorporating heterocycles are linked together through azomethine (-CH=N-) grouping and to study their CNS depressant activity.

MATERIAL AND METHODS

Chemicals and Instrument

o-fluoro aniline, ethyl cyanoacetate, p-methoxy acetophenone, sulphur, 4'-di methyl amino benzaldehyde,4'-hydroxy benzaldehyde,2'-nitro benzaldehyde, 3'-nitro benzaldehyde, 3',4',5'-trimethoxy benzaldehyde, 2'-hydroxy benzaldehyde, 4'-hydroxy 3'-methoxy benzaldehyde, 2'-chloro benzaldehyde, 4'-methoxy benzaldehyde, 3',4'-dimethoxy, 4'-chloro benzaldehyde, 4'-methyl benzaldehyde were obtained from local dealer.

Analytical TLC was performed on Silica plates- GF254 (Merck) with visualization by UV or iodine vapors. Melting points were determined in open capillaries on a Thermonic Melting point apparatus and are uncorrected. The IR spectra (KBr, λ Max, cm^{-1}) were run on Perkin Elmer FTIR Spectrophotometer. 1H-NMR (in $CDCl_3$ / DMSO-*d6*) spectra were recorded using AMX-400 with TMS as internal standard. MS spectra were recorded on Brucker DPX 200. Elemental analyses were performed on Carlo Erba 1108 elemental analyzer and were within ± 0.4% of theoretical values. All the chemicals used were of analytical grade.

Synthesis of 2-cyano-N-(o-fluorophenyl)-acetamide

Condensation of equimolar o-fluoro aniline and ethyl cyanoacetate at a temperature of 170^0-180^{0}C for 7 hours and cooled overnight to yield the 2-cyano-N-(o-fluorophenyl)-acetamide. Yield 45 %

Synthesis of 2-amino-N-(o-fluorophenylcarboxamido)-4-(p-methoxyphenyl) thiophene (I)

A mixture of para methoxy acetophenone (6gm, 0.04mol), 2-cyano-N-(o-fluorophenyl)-acetamide (6.64gm, 0.04 mol), ammonium acetate (1gm) and glacial acetic acid (2 ml) in benzene (100 ml) was refluxed for 12 hours in Dean Stark apparatus with continuous separation of water. After 12 hours the reaction mixture was cooled. On cooling the liquid reaction mixture turned to fine crystalline solid which was employed for further reaction.

To a mixture of the above crude intermediate, sulphur (0.04 mol) in ethanol (40 ml) and diethyl amine (4.0 ml) was added drop wise with stirring. The mixture was stirred for 3 hours at 45–50 °C, chilled overnight and poured. Poured ice cold water on the reaction mixture drop by drop, the solid obtained was filtered washed with ethanol to yield yellow crystalline solids. Recrystallized from alcohol. Yield 40%.

General method for synthesis of 2-[(substituted benzylidene)amino]-N-(o-fluorophenylcarboxamido)-4-(p-methoxyphenyl) thiophene (I a-l):

A mixture of the starting compound **(I)** (0.005 M) and the required substituted aryl aldehydes (0.005 M) in propan-2-ol (30 ml) and catalytic amount of glacial acetic acid (2-5 drops) was heated on microwave irradiation for 2-3 minutes at 340 watts. The reaction mixture was allowed to cool. Solid obtained was filtered, washed with ethanol, dried and crystallized using DMF: Water in a ratio of (4:1) to get the pure title compounds (I a –l).

2-(4-(dimethylamino)benzylideneamino)-N-(2-fluorophenyl)-4-(4methoxyphenyl) thiophene-3-carboxamide Ia

M.P. 120^{0}C; yield: 52%; MS: 473(100%),395(20%),362(60%),340(80%)229(30%);IR max cm^{-1} : 3335.82 (-NH); 3065.79 (Ar-CH); 2916.36 (Ali-CH); 1679.33 (C=O); 1620.30 (-NH bend); 1524.65 (Ar C=C); 1648.61(HC=N);1207.15(C-F);871.09(C-N);751.89(C-S);2959.13(CH,CH_3). ^{1}HNMR(CDCl3):δ=8.6 (1H,s,N=CH);8.5(1H,s.CONH),7.9(2H,m,Aromatic);7.37.5(3H,m,aromatic) 7.1-7.3(3H,m,aromatic);6.9-7.1(4H,m,aromatic) ; 6.85 (1H,s,thiophenering); 3.7 (3H,s,OCH_3) ; 2.8(6H,s,$2CH_3$); ^{13}C NMR: 40.53(Cof CH3);55.9(C of OCH3);118-140(C,aromatic ring);140(2C of thiophene ring); 127(C,thiophenering); 160(C,thiophenering), 163(C,CONH);164(C,N=CH);163(C attached to F); Elemental analysis: C-68.34%,H-5.2%,F-4%,N-8.6,O-6.8%,S-6.6%

2-(4-hydroxybenzylideneamino)-N-(2-fluorophenyl)-4-(4-methoxyphenyl)thiophene-3- carboxamide Ib

M.P. 105 0C; yield: 50%;MS:446 (80%),340(100%),262(50%),151(65%);IR max cm-1: 3423.39 (OH); 3277.08 (-NH str); 3085.05 (Ar-CH); 2936.52 (Ali-CH);

1663.60 (C=O); 1600.57 (-NH bend); 1505.11 (ArC=C);1643.67(HC=N);1215.12(C-F);872.35(C-N);756.50(C-S);

^{1}HNMR (CDCl3) : δ=8.8(1H,s,N=CH); 8.45(1H,s.CONH), 7.6-7.75(3H,m,Aromatic);7.4- 7.59 (2H,m,aromatic) ; 7.2-7.39 (4H,m,aromatic); 7-7.1(3H,m,aromatic);6.9 (1H,s,thiophene ring);5(1H,s,OH);3.7(3H,s,OCH3);

^{13}CNMR:55.9(C,OCH3);118-140(C, aromaticring);140(2Cofthiophene ring);127(C, thiophenering);160.3 (C of thiophene ring), 164 (C,CONH);160(C,N=CH);160.8(C attached to OH);163(C attached to F);

Elemental analysis: C- 67.34%,H-4.2%,F-4%,N-6.6,O-10.8%,S-7.6%

2-(2-nitrobenzylideneamino)-N-(2-fluorophenyl)-4-(4-methoxyphenyl)thiophene-3-carboxamide Ic

M.P. 111 ^{0}C; yield:51%;MS:475(100%),397(70%),364(40%)340(80%),286(20%);IR max cm^{-1}: 3286.64 (-NH); 3083.76 (Ar-CH); 2940.79 (Ali-CH); 1680.00 (C=O); 1627.66 (-NH bend); 1499.90 (Ar C=C); 1648.10 (HC=N); 1218.18 (C-F); 814.20(C-N); 733.74 (C-S); 1350.12 (N-O of NO_2).

^{1}HNMR (CDCl3) : δ= 8.8(1H,s,N=CH); 8.6(1H,s.CONH), 7.5-7.7(2H,m,Aromatic); 7.4-7.9 (3H,m,aromatic); 7.0-7.4 (4H,m,aromatic); 6.9-7.0 (3H,m,aromatic); 6.91 (1H,s,thiophenering) ; 3.7(3H,s,OCH_3);

^{13}C NMR: 54.65 (C of OCH3); 118-140 (C, aromatic ring); 140.23(2Cofthiophene ring); 127.3 (C of thiophene ring); 160.3 (C of thiophene ring), 163.1 (C,CONH); 164 (C,N=CH); 163.8 (C attached to F); Elemental analysis: C- 63.19%,H-3.7%,F-4.1%,N-8.5,O-13.8%,S-6.56%

2-(3-nitrobenzylideneamino)-N-(2-fluorophenyl)-4-(4-methoxyphenyl)thiophene-3-carboxamide Id

M.P. 113 ^{0}C; yield:43%;MS:475(100%),364(50%),286(70%);IR max cm^{-1}: 3287.74 (-NH); 3074.32 (Ar-CH); 2940.79 (Ali-CH); 1675.00 (C=O); 1630.33 (-NH bend); 1490.56 (Ar C=C); 1668.42 (HC=N); 1215.15 (C-F); 815.15(C-N); 735.65 (C-S); 1360.01 (N-O of NO_2)

^{1}HNMR (CDCl3): δ=8.9 (1H,s,N=CH); 8.45(1H,s.CONH), 7.6-7.7 (2H,m,aromatic); 7.4-7.6 (4H,m,aromatic); 7.2-7.56 (3H,m,aromatic); 7.1-7.2 (3H,m,aromatic); 6.92 (1H,s,thiophene ring); 3.7(3H,s,OCH_3);

^{13}C NMR: 55.65(C,OCH3);118-140(C, aromatic ring);140.5(2C of thiophene ring);127(C of thiophene ring);160.1 (C of thiophene ring), 163.5(C,CONH);164.8(C,N=CH);163.3(C attached to F);

Elemental analysis: C- 63.34%,H-3.6%,F-4.3%,N-8.5,O-13.8%,S-6.56%

2-(3,4,5-trimethoxybenzylideneamino)-N-(2-fluorophenyl)-4-(4-methoxyphenyl)thiophene-3-carboxamide Ie

M.P. 119 0C; yield:45%;MS:430(100%),250(50%),319(80%),241(60%);IR max cm-1 : 3332.74 (-NH); 3077.59 (Ar-CH); 2926.10 (Ali-CH); 1660.21 (C=O); 1618.26 (-NH bend); 1534.52 (Ar C=C); 1643.21 (HC=N);1217.21(C-F);1252.58(OCH3),872.10(C-N);749.54(C-S);

^{1}HNMR(CDCl3):δ=8.9(1H,s,N=CH); 8.5 (1H,s.CONH),7.4-7.9 (5H,m,Aromatic); 7.3-7.39 (2H,m,aromatic); 7.1-7.3 (3H,m,aromatic); 6.9 (1H,s,thiophenering); 3.7 (12H,s,3OCH3); ^{13}CNMR:56.53 (CofOCH3);55.9(CofOCH3);118-140(C,aromaticring);140.3(2C,thiophene ring);127.1(C of thiophene ring);160.5 (C of thiophene ring), 163.7(C,CONH);164.1(C,N=CH);163.3(C attached to F); Elemental analysis: C- 64.54%,H-4.82%,F-3.4%,N-5.6,O-15.38%,S-6.16%

2-(2-hydroxybenzylideneamino)-N-(2-fluorophenyl)-4-(4-methoxyphenyl)thiophene-3-carboxamide If

M.P. 112 ^{0}C; yield: 49%;MS:446(100%),340(85%),229(70%)151(40%);IR max cm^{-1}: 3423.39 (OH); 3277.08 (-NH); 3085.05 (Ar-CH); 2936.52 (Ali-CH); 1663.60 (C=O); 1600.57 (-NH bend); 1505.11 (Ar C=C);1643.67(HC=N);1215.12(C-F);872.35(C-N);756.50(C-S);

^{1}HNMR(CDCl3):δ=8.6(1H,s,N=CH);8.45(1H,s.CONH),7.6-7.7(2H,m,Aromatic);7.3-7.58 (3H,m,aromatic); 7.1-7.3 (3H,m,aromatic);6.9-7.1 (4H,m,aromatic); 6.8 (1H,s,thiophene ring);5.2(1H,s,OH); 3.7(3H,s,OCH_3);

^{13}C NMR:55.9(C of OCH3);118-140(C, aromatic ring);140(2C of thiophene ring);127(C of thiophene ring);160 (C of thiophene ring), 163(C,CONH);164(C,N=CH);163(C attached to F).165.1(C attached to OH);

Elemental analysis: C- 67.34%,H-4.25%,F-4.24%,N-6.6,O-10.8%,S-7.16%

2-(4-hydroxy-3-methoxybenzylideneamino)-N-(2-fluorophenyl)-4 (4methoxyphenyl)thiophene-3-carboxamide Ig

M.P 107 ^{0}C; yield:46%;MS:476(100%),340(70%),365(60%),287(50%); IR max cm^{-1}: 3433.23 (OH); 3278.12 (-NH); 3062.99(Ar-CH); 2955.12 (Ali-CH); 1654.21 (C=O); 1615.61 (-NH bend); 1512.14 (Ar C=C); 1650.77 (HC=N); 1256.21 (OCH_3) 1221.43 (C-F);875.43(C-N);754.34 (C-S);

^{1}HNMR(CDCl3): δ=8.8(1H,s,N=CH); 8.4 (1H,s.CONH), 7.7-7.8 (2H,m,aromatic);7.5-7.7 (2H,m,aromatic); 7.4-7.49 (2H,m,aromatic); 7.1-7.35 (2H,m,aromatic);7-7.1 (2H,m,aromatic); 6.85 (1H,s,thiophenering); 5 (1H,s,OH); 3.5 (6H,s,OCH_3);

^{13}CNMR:57.53(C,OCH3);55.9(C,OCH3);118-140(C, aromatic ring);140.2 (2C of thiophene ring); 127.4 (C, thiophenering); 160.4 (C, thiophene ring), 163.9 (C,CONH); 164.1 (C,N=CH) ; 163.1 (C attached to F); 160.3 (C attached to OH); Elemental analysis: C-65.34%,H-4.2%,F-3.44%,N-5.76,O-13.38%,S-6.76%

2-(2-chlorobenzylideneamino)-N-(2-fluorophenyl)-4-(4-methoxyphenyl)thiophene-3 carboxamide Ih

M.P. 114^{0}C;yield:52%;MS:464(100%),353(60%),229(50%),151(70%); IR max cm^{-1}: 3231.25 (-NH); 3056.22 (Ar-CH); 2923.32 (Ali-CH); 1667.32(C=O); 1634.12 (-NH bend); 1523.14 (Ar C=C); 1650.41 (HC=N); 1241.28 (C-F); 831.26(C-N); 742.53 (C-S); 641.91 (C-Cl),

^{1}H NMR (CDCl3): δ=8.6(1H,s,N=CH);8.5(1H,*s* of amide),7.9(2H of aromatic);7.5-7.9(7H,m, aromatic) 7.1-7.5(3H,aromatic)6.9(1H of thiophene ring); 3.7(3H,s,OCH_3);

^{13}C NMR: 55.9(C of OCH3);118-140(C, aromatic ring);140.1(2C of thiophene ring);127.3(C of thiophene ring);160.1 (C of thiophene ring), 163.3(C,CONH);164.7(C,N=CH);163(C attached to F); Elemental analysis: C- 64.34%, H-3.2%,F-4%,N-6.6,O-6.8%,S-6.86%

2-(4-methoxybenzylideneamino)-N-(2-fluorophenyl)-4-(4-methoxyphenyl)thiophene-3-carboxamide Ii

M.P.109^{0}C;yield:42%;MS:460(100%),382(70%),340(50%),229(30%);Irmaxcm^{-1}:3282.41(-NH); 3065.13 (Ar-CH); 2945.12 (Ali-CH); 1653.00 (C=O); 1613.62 (-NH bend);1518.51 (Ar C=C); 1633.43 (HC=N);1221.18 (OCH_3) 1216.16 (C-F); 878.52 (C-N); 758.51(C-S);

^{1}HNMR(CDCl3):δ=8.7(1H,s,N=CH);8.45(1H,s.CONH),7.5-7.7(2H,m,Aromatic);7.3-7.5 (3H,m,aromatic), 7.1-7.3(3H,m,aromatic) ;6.9-7.1 (4H,m,aromatic); 6.85 (1H,s,thiophene ring); 3.7 (6H,s,OCH_3);

^{13}C NMR: 53.53(C,OCH3);55.9(C,OCH3);118-140(C, aromatic ring);140.1(2C of thiophene ring); 127 (C of thiophene ring) ; 160(C of thiophene ring), 163 (C,CONH) ; 164 (C,N=CH) ;163(C attached to F); Elemental analysis: C- 67.84%,H-4.52%,F-4.13%,N-6.06,O-10.8%,S-6.76%

2-(3,4-dimethoxybenzylideneamino)-N-(2-fluorophenyl)-4-(4-methoxyphenyl)thiophene-3-carboxamide Ij

M.P. 121 ^{0}C; yield:53%; MS:490(100%), 379(50%), 329(40%), 340(70%), 150(10%); IR max cm^{-1}: 3277.08 (-NH str); 3043.13 (Ar-CH); 2933.18 (Ali-CH); 1659.42 (C=O); 1616.61 (-NH bend);1516.23 (Ar C=C); 1653.84 (HC=N); 1243.58 (OCH_3) 1215.12 (C-F); 873.61(C-N); 750.44(C-S); ^{1}HNMR(CDCl3):δ=8.6(1H,s,N=CH); 8.3(1H,s.CONH),7.6-7.9(2H,m,Aromatic); 7.4-7.55(4H,m,aromatic) 7.2-7.35(3H,m,aromatic); 7.0-7.1 (2H,m,aromatic); 6.9 (1H,s,thiophenering); 3.8(9H,s,OCH_3);

^{13}CNMR:56.53(C,OCH3);55.9(C,OCH3);118-140.1(C,aromaticring);140.4(2C,thiophene ring); 127.4 (C,thiophene ring); 160.8 (C, thiophene ring), 163.65 (C,CONH);164.1 (C,N=CH); 163.4 (C attached to F); Elemental analysis: C- 66.14%,H-4.72%,F-3.84%,N-5.6,O-13.08%,S-6.56%

2-(4-chlorobenzylideneamino)-N-(2-fluorophenyl)-4-(4-methoxyphenyl) thiophene-3-carboxamide Ik

M.P. 115 ^{0}C; yield: 48%; MS: 464(100%),353(60%),229(50%),151(70%);

IR max cm^{-1}: 3213.18 (-NH); 3072.34 (Ar-CH); 2921.16 (Ali-CH); 1668.66(C=O); 1628.51 (-NH bend); 1527.21 (Ar C=C); 1656.25 (HC=N); 1241.13 (C-F); 821.89 (C-N); 789.51 (C-S); 692.71 (C-Cl).

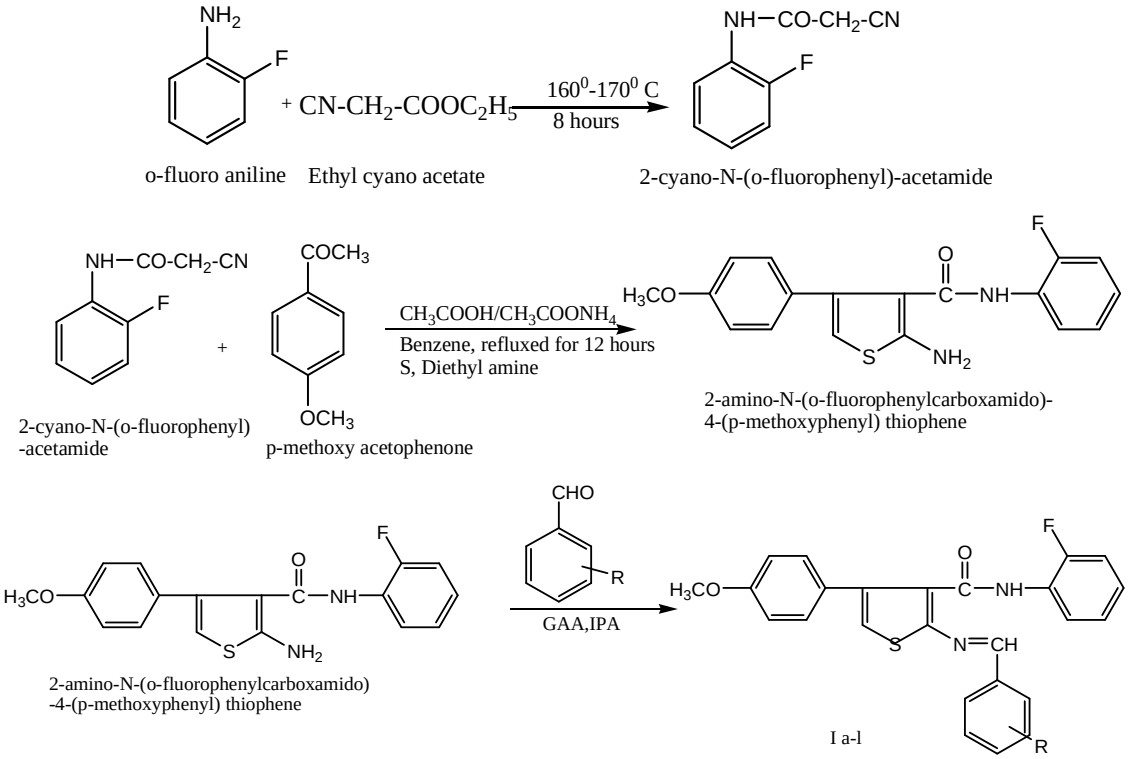
^{1}HNMR(CDCl3):δ=8.7(1H,s,N=CH);8.45(1H,s.CONH),7.5-7.8(3H,m,Aromatic);7.3- 7.5 (3H,m,aromatic); 7.1-7.3 (3H,m,aromatic); 6.9-7.1 (3H,m,aromatic); 6.9(1H,s,thiophene ring) 3.7(3H,s,OCH_3);

^{13}CNMR: 55.9(C,OCH3);118-140(C,aromatic ring);140(2C,thiophene ring);127.7(C, thiophene ring); 160.6(C,thiophene ring), 163.5(C,CONH);164.7(C,N=CH);163(C attached to F);167.3(C attached to Cl); Elemental analysis: C- 66.12%,H-4.71%,F-..79%, N-5.76, O-13.02%, S-6.53%

2-(4-methylbenzylideneamino)-N-(2-fluorophenyl)-4-(4methoxyphenyl)thiophene-3-carboxamide Il

M.P 123 ^{0}C; yield:47%;MS:460(100%),356(70%),245(80%),111(30%); IR max cm^{-1}: 3256.22 (-NH); 3083.15 (Ar-CH); 2951.15 (Ali-CH); 1646.17 (C=O); 1609.84 (-NH bend); 1595.03 (Ar C=C); 1634.43(HC=N);1252.63(OCH_3),1262.82(C-F);873.18(C-N);755.63(C-S); ^{1}HNMR(CDCl3):δ=8.6(1H,s,N=CH);8.5(1H,s.CONH),7.2-7.56(3H,m,Aromatic);7.1-7.2 (3H,m,aromatic); 7.0-7.19(3H,m,aromatic);6.9-7.0(3H,m,aromatic);6.85(1H,s,thiophene ring);3.8(6H,s,OCH_3);

^{13}CNMR:55.53(C,OCH3);55.9(C,OCH3);118-140(C, aromatic ring); 140(2C,thiophene ring); 127.1 (C, thiophene ring); 160 (C, thiophene ring),163.8 (C,CONH);164 (C,N=CH);163.4 (C attached to F); Elemental analysis: C- 70.34%,H-4.72%,F-4.26%,N-6.26,O-7.18%,S-7.26%



R = 4'-dimethyl amino,4'-hydroxy, 2'-nitro,3'-nitro,3',4',5'- tri methoxy, 2'-hydroxy, 4'-hydroxy 3'- methoxy,2'-chloro, 4'-methoxy, 3',4'-di methoxy,4'-chloro,4'-methyl

Fig. 1: General Experimental scheme for the synthesis of Ia-l

Table 1: Physical Data I a-l

Comp No.	R	M.P	% Yield	R *f*
Ia	4,-dimethyl amino	120	52	0.65
I b	4'-hydroxy	105	50	0.73
I c	2'-nitro	111	51	0.65
I d	3'-nitro	113	43	0.69
Ie	3',4',5'- tri methoxy	119	45	0.66
I f	2'-hydroxy	112	49	0.54
I g	4'-hydroxy3'-methoxy	107	46	0.72
I h	2'-chloro	114	52	0.55
I i	4'-methoxy	109	42	0.67
I j	3',4'-di methoxy	121	53	0.74
I k	4'-chloro	115	48	0.59
I l	4'-methyl	123	47	0.64

Experimental animals

Albino mice (18-25 g) of either sex were used in these experiments. Animals were provided with standard food and water ad libitum and were maintained at a temperature of 25±2°C, humidity of 55±5% and with 12 h light – dark cycle. All the experimental protocols were approved by Institutional Animal Ethics Committee (IAEC) of PES College of Pharmacy and were conducted according to the guidelines of CPCSEA, India.

Pharmacology

Acute toxicity test

Compounds were investigated for acute toxicity study (LD50) according to method of Smith[13]. Compounds were administered imp. In doses of 50, 100, 200, 500, 1000, 1500 and 2000 mg/kg to different groups of mice, each group consisting of six animals (n = 6). The mortality rate was observed and recorded for a 24 hr period.

The compounds that showed CNS depressant activity were investigated for acute toxicity study (LD50) according to the method. It was found that, these compounds are safe at the chosen dose (100 mg/ kg).

CNS Depressant activity

The title derivatives (Ia–l) were evaluated for CNS depressant activity by determination of pentobarbitone induced sleeping time method and photoactometer at a dose of 100 mg/kg in albino mice.

Determination of pentobarbitone induced sleeping time

In this method, mice of either sex were randomly taken and divided into control, standard and different test groups, each group contain six animals. Group I served as control and treated with normal saline (10 ml/kg, i.p.), group II (standard) treated with standard drug chlorpromazine hydrochloride (3mg/kg, i.m.) 15 min before the administration of pentobarbitone (40mg/kg, i.p.). Test groups were treated with the title compounds I a-l (100mg/kg, imp). Pentobarbitone (40mg/kg, i.p.) was administered 30 min later. Onset of sleep and duration of sleep measured for the entire group. Onset of action was recorded by noting the time of loss of reflex for three consecutive trials, duration of sleep recorded by time difference between loss of righting reflex and recovery time.

The observation of activity are shown in Table 2

Table 2: CNS Depressant activities by pentobarbitone induced sleeping time method I a- l

Compound	R	Dose mg/kg	Onset of sleep (mins)	Duration of sleep (mins)
Control(Saline)		----------	10.75±0.63	45.25±1.04
Chlorpromazine	----------	3	4.75±0.48	128.25±1.89
I a	4'-dimethyl amino	100	7.75±0.45	56.00±1.87
I b	4'-hydroxy	100	8.67±0.29	55.50±2.06
I c	2'-nitro	100	9.00±0.205	45.75±2.135
I d	3'-nitro	100	8.75±0.79	50.25±2.55
I e	3',4',5'-tri methoxy	100	5.25±0.855	108.25±1.03
I f	2'-hydroxy	100	7.55±0.48	71.75±1.88
I g	4'-hydroxy3'-methoxy	100	6.00±0.41	93.50±1.89
I h	2'-chloro	100	7.25±0.48	70.25±2.17
I i	4'-methoxy	100	4.95±0.25	100.5±3.07
I j	3',4'-di methoxy	100	5.23±0.25	97.75±1.84
I k	4'-chloro	100	7.75±0.43	61.00±1.58
I l	4'-methyl	100	5.50±0.29	96.25±0.95

Values are expressed in Mean±SEM, n = 6, p<0.001

CNS depressant activity by photoactometer method

The CNS depressant activity of the title compounds were evaluated by studying locomotor activity of mice using photoactometer [25]. Briefly, Albino mice of either sex (20 – 25 g) were randomly divided into control, standard and different test groups, each group contain six animals. The mice were placed individually inside the chamber of photoactometer for 10 min and basal activity score was noted. Group I was treated with vehicle (0.5% sod. CMC) and standard drug diazepam (5 mg/kg, i.p.) administered to group II. The animals of the test group were treated with compounds I a-l (100 mg/kg, i.p.). After 20 min of administration of test compound, the animals were kept into the photoactometer chamber and the counts were noted for 10 min after a 10 min rest in the chamber. The same procedure was repeated after 50 min. Percent decrease in activities were calculated for each group using the formula,

Percent decrease in activity=(1-Wa/Wb)X100, where Wa and Wb are average activity scores after and before administration of test compound respectively and average decrease in activity was calculated for all groups.

The observation of activity shown in table 3

Table: 3 CNS depressant activities by photoactometer

Compound	Dose Mg/kg	Photoactometer counts			% CNS depressant activity	
		Prior (control) administration of test compound	30 min after administration of test compound	60 min after administration of test compound	After 30 min	After 60 min
Diazepam	5	103±1.67	15±1.21	11±1.17	85.43	89.32
Ia	100	98±1.73	24±1.23	20±1.25	75.51	79.59
Ib	100	104±1.75	33±1.40	25±1.35	68.26	75.96
Ic	100	103±1.75	37±1.20	24±1.67	64.07	76.69
Id	100	97±1.73	32±1.37	23±1.56	67.01	76.28
Ie	100	95±1.75	22±1.42	15±1.28	76.87	84.00
If	100	110±1.76	35±1.21	27±1.18	68.18	75.10
Ig	100	108±1.67	27±1.75	18±1.51	75	83.30
Ih	100	115±1.56	35±1.19	27±1.23	69.56	76.00
Ii	100	101±1.23	23±1.17	17±1.23	77.22	83.16
Ij	100	96±1.37	24±1.72	19±1.73	75	80.20
Ik	100	100±1.72	35±1.35	27±1.23	65	73.00
Il	100	105±1.52	23±1.18	19±1.13	78	81.11

Values are expressed in Mean±SEM, n = 6, p<0.001

RESULTS

Twelve derivatives were synthesized and their structure was confirmed by IR, NMR, mass spectrum and elemental analysis.

All the twelve derivatives were subjected to CNS depressant activity by pentobarbitone induced sleeping time (Table2) shown increase in sleeping time and photoactometer method (Table 3) shown decrease in locomotor activity.

All the derivatives showed moderate to mild activity. The five derivatives (Ie, Ig, Ii, Ij and Il) showed a comparable increase in sleeping time with chlorpromazine the standard drug used for pentobarbitone induced sleeping time method, and after 60 minutes of administration of these drugs it showed a range of 80 % to 84% decrease in locomotor activity when compared to standard drug diazepam (89.32%).

DISCUSSION

The formation of the starting compound was confirmed by IR spectra where it shows $-NH_2$ peak at 3403.0 cm-1. The NMR spectrum shows a peak at δ (ppm) = 5 of free NH_2 group in the compound. The IR spectra of all the Schiff bases (I a-l) show the disappearance of $-NH_2$ peak and the appearance of –N=CH (Imine) peak at a range of 1690-1640 cm-1, which clearly suggest the formation of the expected compounds. The NMR spectra of the compounds show sharp singlet peak at δ (ppm) =8.9-8.5 of –N=CH (Imine-H) which also further confirm the formation of the compounds of the series. The title compounds were also confirmed by Mass spectra. In CNS depressant activity it is seen from the table 2 and table 3 that all the derivatives having moderate to mild activity whereas the derivatives (Ie, Ig, Ii, Ij and Il) having electron donating group on the benzylidene ring shows comparable activity with the standard drugs.

CONCLUSION

The title compounds (I a-l) were prepared from the starting compound 2-amino-N-(o-fluoro phenylcarboxamido)-4-(p-methoxyphenyl) thiophene (I) and screened for CNS depressant activity. Among all compounds it was found that derivatives having electron donating group such as methoxy, methyl (Ie, Ig, Ii, Ij and Il) were showing comparable activity when compared to standard drugs.

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