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QSAR study, synthesis and anti-depressant studies of some novel schiff base derivatives of benzothiazepine

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This study was designed to synthesize, characterize and evaluate the pharmacological activity of schiff base derivatives of benzothiazepine. Purity of the synthesized compounds was ascertained by TLC and melting points were determined by an open capillary tube method. The compounds were characterized by IR, NMR and mass spectroscopic methods. Antidepressant activity of all synthesized compounds was evaluated by despair swim test using *Sprague Dawley Rats*. Standard drug imipramine was used as the control. In the despair swim test, all synthesized derivatives showed antidepressant activity. QSAR for the title compounds was performed using TSAR 3.3 software and results were found satisfactory. These results are useful for the future investigations.

Keywords: Antidepressant activity, Despair swim test, QSAR, *Sprague Dawley Rat.*

INTRODUCTION

As estimated by WHO, depression shall become the second largest illness in terms of morbidity by another decade in the world; already one out of every five women, and every twelve men have depression. Not only adults, but two percent of school children, and five percent of teenagers also suffer from depression, and these mostly go unidentified. Depression has been the commonest reason why people come to a psychiatrist, although the common man's perception is that all psychological problems are depression [1-2]. Current treatments for depression either fail to produce recovery or induce unwanted side effects. So there is still a large unmet clinical need [3-5]. The main aims in the development of new antidepressants are greater efficacy, absence of side effects, lack of toxicity in over dose and earlier onset of action [7]. Elaborate research work has been carried out in the past and continues in the present to synthesize new compounds to meet depression. The forced swim test (behavioral despair test) in the rat is widely used for the initial screening of antidepressants. These tests have good predictive validity and allow rapid and economical detection of substances with potential antidepressant-like activity. The majority of clinically used antidepressants decrease the duration of immobility [4].

EXPERIMENTAL

Materials &Methods

Melting points were determined by an open capillary method and are uncorrected. The ^{1}H-NMR spectra were recorded on the sophisticated multinuclear FT-NMR spectrometer model Advance-II (Bruker) using dimethylsulfoxide-*d*6 as solvent and tetramethylsilane as internal standard. IR spectra were recorded on Jasco FT-IR-spectrophotometer using KBr disc method. Antidepressant activity of all synthesized compounds was evaluated by despair swim test using *Sprague Dawley Rats*. Pharmacological screening values therein were converted into log (% Inh) and were used for multiple correlation analysis with descriptors generated using TSAR 3.3 software.

QSAR Methodology

All molecules were drawn in Chem draw ultra 8.0 module in Chemoffice 2004 software and imported into TSAR software. Charges were derived using Charge 2-Derive charges option and optimized by using Cosmic-optimize 3 D option in the structure menu of the project table. Substituents were defined and descriptors were calculated for the whole molecule as well as for the substituents. Several equations were generated correlating both log (% Inh) with physicochemical parameters (descriptors) by multiple linear regression analysis

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(MLR) method. Data was standardized by range and one method was used for cross validation. Models were excluded if correlation was exceeding 0.9 for more rigorous analysis. Correlation matrix was generated to find any intercorrelation between the descriptors. Intercorrelation between the descriptors in the final equation was less than 0.2 [7].

Pharmacology: Rat-Sprague Dawley (220-255 gm), 8-12 weeks old, were obtained from the National Institute of Bioscience, Pune. They were housed in autoclaved polypropylene cages in groups of 2-3 rats per cage and kept in a room maintained at 19 to 25 ^{0} C and humidity 45 to 65 % with a 12-h light/dark cycle. They were allowed to acclimatize for four days before the experiments and were given free access to a standard sterilized extruded rodent diet provided *ad libitum.* Reverse osmosis water treated with UV light was provided *ad libitum* in autoclaved polypropylene bottles and autoclaved corn cob was used as bedding material.
All procedures of the present study were in accordance with the standard operating procedures of the Prado Pvt. Ltd. guidelines provided by the Committee for the Purpose of Control and Supervision of Experiments on Animals (CPCSEA) as published in The Gazette of India, December 15, 1998. Prior approval of the Institutional Animal Ethics Committee (IAEC) was obtained before initiation of the study (IAEC-13-004)

Antidepressant Activity (Forced Swim Test in Rat):

Behavioral despair or forced swim test (FST) was proposed as a model to test antidepressant activity by Porsolt et al. [8]. It was suggested that mice or rats when forced to swim in a restricted space from where they cannot escape are induced to a characteristic behavior of immobility. This behavior reflects a state of despair which can be reduced by several agents which are therapeutically effective in human depression. The behavioral despair test is employed to assess the antidepressant activity of synthesized derivatives. *Sprague-Dawley rats* of 200-270 g in a group of two each were used and on the first day of the experiment (pretest session), rats were individually placed in a cylindrical recipient (plexiglass cylinder) of dimensions (diameter, 10 cm; height, 25 cm) containing 10 cm of water at 25°C. The animals were left to swim for 6 min before being removed, dried and returned to their cages. The procedure was repeated 24 h later, in a 5 min swim session (test session). The synthesized compounds (25 mg kg-1), and imipramine, as a reference antidepressant drug (25 mg kg^{-1}) were suspended in a 0.5 % aqueous solution of Na CMC (carboxy methyl cellulose). The drugs were given by gavage in a standard volume of 10 ml/kg body weight, 1 h prior to the test. Control animals received 0.5 % aqueous solution of Na CMC. This test was performed after 1 h, 5 h and 24 h of dose administration. For individual animals video recording was made. Then, the rats were dropped individually into the plexiglass cylinder and left in the water for 6 min. After the first 2 min of the initial vigorous struggling, the animals were immobile. Immobility time is the time spent by rat floating in water without struggling, making only those movements necessary to keep the head above the water. The total duration of immobility was recorded during the last 5 min of the 6 min test session.

Step I: Synthesis of ethyl-4-methyl-2-substituted -2,5-dihydro-1,5-benzothiazepine-3 carboxylate.

An equimolar mixture of 2-aminothiophenol, substituted benzaldehydes and ethyl acetoacetate, in 20 ml ethyl alcohol was refluxed for 50 min at 70-90^0 C. Completion of the reaction was monitored by TLC [eluent: ethyl acetate/petr. ether (3:7)]. After completion of the reaction, the reaction mixture was poured onto crushed ice; the solid crude product was washed with water. The crude product was purified by recrystallisation with hot ethanol. (I_1)

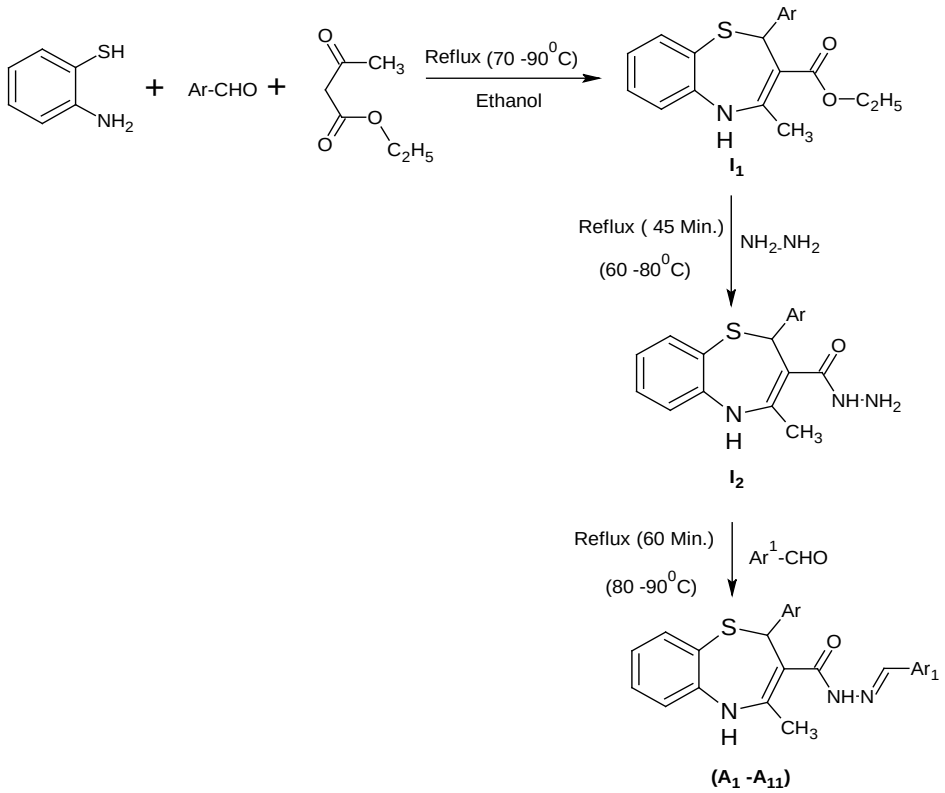
Step II: Synthesis of 4-methyl-2-substituted -2,5-dihydro-1,5-benzothiazepine-3-carbohydrazide

A mixture of 0.01 mole of **I_1** and 0.01 mole of hydrazine was added in 05 ml ethyl alcohol. The reaction mixture was refluxed at 60-80 ^{0} C for 45 min. The reaction mixture was cooled to room temperature, the residue was poured onto crushed ice and the solid separated was filtered and dried through pump to afford the corresponding 4-methyl-2-substituted-2,5-dihydro-1,5-benzothiazepine-3-carbohydrazide. (I_2)

Step III: Synthesis of 4-methyl-2-phenyl-N'-[(E)-phenylmethylidene]-2,5-dihydro-1,5-benzothiazepine-3-carbohydrazide

A mixture of 0.01 mole of **I_2** and 0.01 mole of substituted benzaldehydes was added in 05 ml ethyl alcohol. The reaction mixture was refluxed at 80-90 ^{0} C for 60 min. The reaction mixture was cooled to room temperature, the residue was poured onto crushed ice and the solid separated was filtered and dried through pump to afford the corresponding schiff base derivatives of 1,5-benzothiazepine. **(A_1-A_{11}).**

Scheme



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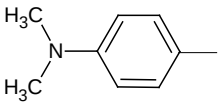
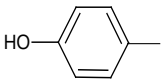
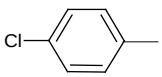
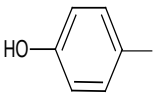
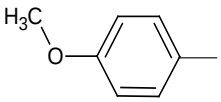
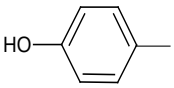
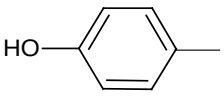
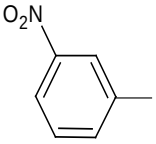
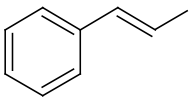
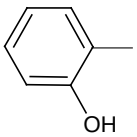
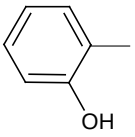
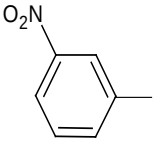
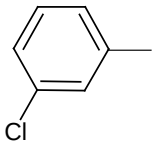
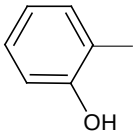
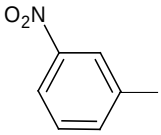
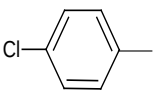
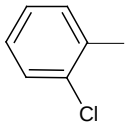
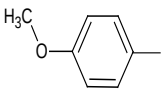
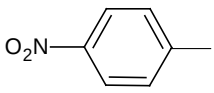
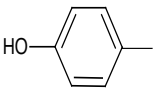
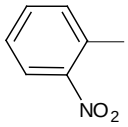
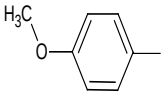
A_1			A_7		
A_2			A_8		
A_3			A_9		
A_4			A_{10}		
A_5			A_{11}		
A_6					

Spectral data

A_1: IR (KBr) cm^{-1}: 3213.45 (-NH str.), 3010.23 (Ar-CH str.), 1682.11 (-C=O str.), 1525.32 (-C=N str), 3565.23 (-OH str.), 1245.36 (-C-N str). ^1H NMR: 4.50 (1H thiazipine), 8.54 (1H–N=CH), 9.61 (1H –NH sec. amine), 8.54 (1H–NH sec. amide), 9.43 (1H–OH), 6.8-7.2 (12H phenyl), 3.66 (3H–CH_3,–C-N), 2.26 (3H CH_3). m/e(100%): 367.14

A_2: IR (KBr) cm^{-1}: 3010.23 (Ar-CH str.), 1682.11 (-C=O str.), 3213.45 (-NH str.), 1525.32 (-C=N str), 1245.36 (-C-N str), 3600.24 (-OH str.), 1260.02 (-C-O str). ^1H NMR: 4.50 (1H thiazipine), 8.54 (1H–N=CH), 9.61 (1H–NH sec. amine), 8.54 (1H–NH sec. amide), 9.43 (1H–OH), 6.8-7.2 (12H phenyl), 2.26 (3H CH_3). m/e(100%): 353.13

A_3: IR (KBr) cm^{-1}: 3310.23 (-CH=CH str.), 3213.45 (-NH str.), 3010.23 (Ar-CH str.), 1682.11 (-C=O str.), 1525.32 (-C=N str), 3650.12 (-OH str.), 1245.36 (-C-N str). ^1H NMR: 6.32-6.53 (-2H –CH=CH), 3.90 (1H thiazipine), 8.54 (1H–N=CH), 9.61 (1H–NH sec. amine), 8.54 (1H–NH sec. amide), 11.43 (1H–OH), 6.8-7.2 (13H phenyl), 2.26 (3H CH_3). m/e(100%): 366.15

A_4: IR (KBr) cm^{-1}: 3213.45 (-NH str.), 3010.23 (Ar-CH str.), 1682.11 (-C=O str.), 1525.32 (-C=N str), 1245.36 (-C-N str), 940.23 (-C-Cl str.), 3620.32 (-OH str.). ^1H NMR: 4.50 (1H thiazipine), 8.54 (1H–N=CH), 9.61 (1H –NH sec. amine), 8.54 (1H –NH sec. amide), 9.43 (1H–OH), 6.8-7.2 (12H phenyl), 3.66 (3H–CH_3, –C-N), 2.26 (3H CH_3). m/e(100%): 371.14

A_5: IR (KBr) cm^{-1}: 3010.23 (Ar-CH str.), 1682.11 (-C=O str.), 1525.32 (-C=N str), 1245.36 (-C-N str), 930.21 (-C-Cl str.), 1260.02 (-C-O str), ^1H NMR: 4.50 (1H thiazipine), 8.54 (1H–N=CH), 9.61 (1H–NH sec. amine), 8.54 (1H–NH sec. amide), 6.8-7.2 (12H phenyl), 2.26 (3H CH_3). m/e(100%): 357.12

A_6: IR (KBr) cm^{-1}: 3213.45 (-NH str.), 3010.23 (Ar-CH str.), 1682.11 (-C=O str), 1525.32 (-C=N str), 1245.36 (-C-N str), 1260.02 (-C-O str), 1255.36 (-N-O str). ^1H NMR: 4.50 (1H thiazipine), 8.54 (1H–N=CH), 9.61 (1H–NH sec. amine), 8.54 (1H–NH sec. amide), 6.8-7.2 (12H phenyl), 3.82 (3H–CH_3, –C-O), 2.26 (3H CH_3). m/e(100%): 355.13

A_7: IR (KBr) cm^{-1}: 3213.45 (-NH str.), 3010.23 (Ar-CH str.), 1682.11 (-C=O str.), 1525.32 (-C=N str), 1245.36 (-C-N str), 940.21 (C-Cl str.), 3600.12 (-OH str.). ^1H NMR: 4.50 (1H thiazipine), 8.54 (1H–N=CH), 9.61 (1H–NH sec. amine), 8.54 (1H–NH sec. amide), 9.43 (1H–OH), 6.8-7.2 (12H phenyl), 3.86 (3H–CH_3, –C-O), 2.26 (3H CH_3).m/e(100%): 331.11

A_8: IR (KBr) cm^{-1}: 3010.23 (Ar-CH str.), 1682.11 (-C=O str.), 1255.36 (-N-O str.), 1525.32 (-C=N str), 1245.36 (-C-N str), 3616.11 (-OH str.). ^1H NMR: 4.50 (1H thiazipine), 8.54 (1H–N=CH), 9.61 (1H–NH sec. amine), 8.54 (1H–NH sec. amide), 9.43 (1H–OH), 6.8-7.2 (12H phenyl), 2.26 (3H CH_3).m/e(100%): 317.09

A_9: IR (KBr) cm^{-1}: 3213.45 (-NH str.), 3010.23 (Ar-CH str.), 1682.11 (-C=O str.), 1525.32 (-C=N str), 1245.36 (-C-N str), 3616.11 (-OH str.).^1H NMR: 4.50 (1H thiazipine), 8.54 (1H–N=CH), 9.61 (1H–NH sec. amine), 8.54 (1H –NH sec. amide), 9.43 (1H–OH), 6.8-7.2 (12H phenyl), 2.26 (3H CH_3). m/e(100%): 315.10

A_{10}: IR (KBr) cm^{-1}: 3010.23 (Ar-CH str.), 1689.78 (-C=O str), 1525.32 (-C=N str), 1245.36 (-C-N str), 1255.36 (-N-O str.), 940.21 (-C-Cl str.). ^1H NMR: 4.50 (1H thiazipine), 8.54 (1H –N=CH), 9.61 (1H–NH sec. amine), 8.54 (1H–NH sec. amide), 6.8-7.2 (12H phenyl), 2.26 (3H CH_3).m/e(100%): 354.14

A_{11}: IR (KBr) cm^{-1}: 3208.12 (-NH2 str.), 3010.23 (Ar-CH str.), 1689.78 (-C=O str), 1525.32 (-C=N str), 1245.36 (-C-N str), 3600.12 (-OH str.). ^1H NMR: 4.50 (1H thiazipine), 8.54 (1H–N=CH), 9.61 (1H–NH sec. amine), 8.54 (1H–NH sec. amide), 9.43 (1H–OH), 6.8-7.2 (12H phenyl), 2.26 (3H CH_3). m/e(100%): 369.15.

Statistical evaluation of the equations is in the accepted range. The correlation coefficient is high with a low standard error. The residual value and residual variance for each series is also low indicating good predictive power of the models. From equation 1 it is observed that two electronic parameters: dipole moment Z component (whole molecule) and VAMP HOMO (whole molecule) negatively contribute (-0.218 and -1.576) for the activity, so electron withdrawing groups may enhance the activity (% Inh).

RESULTS AND DISCUSSION

The structures, yields and melting points of the compounds are given in Table 1. Melting points of the synthesized compounds were sharp indicating that the compounds were pure; the yield values of the compounds also suggested that the chemical methods were reliable for the synthesis of the compound. All compounds showed characteristic peaks in the IR and NMR spectroscopic studies.

Antidepressant Activity

All synthesized compounds were subjected to antidepressant activity study on Sprague-Dawley rats by despair swim test. Imipramine was used as standard control. The results showed that all compounds displayed antidepressant activity. Among them two compounds (A_3 and A_6) showed significant antidepressant activity compared with the standard control imipramine (Table 2).

Table 1. Analytical and physicochemical data of the synthesized compounds (A_1-A_{11}).

Comp. Code	Mol. Formula	Mol. Wt.	M.P. ° C	Yield %	Elemental analyses Calcd (found)		
					C	H	N
A_1	$C_{26}H_{26}N_4O_2S$	458.18	195-200	72	68.10 (67.80)	5.71 (5.50)	10.48 (10.10)
A_2	$C_{24}H_{21}N_3O_3S$	431.13	235-238	75	66.80 (66.50)	4.91 (4.51)	9.74 (9.61)
A_3	$C_{26}H_{23}N_3O_2S$	441.54	205-207	67	70.72 (70.65)	5.25 (5.10)	9.52 (9.23)
A_4	$C_{24}H_{20}ClN_3O_2S$	449.95	230-232	71	64.06 (65.80)	4.48 (4.20)	9.34 (9.05)
A_5	$C_{25}H_{22}ClN_3O_2S$	463.11	202-205	78	64.72 (64.60)	4.78 (4.40)	9.06 (8.95)
A_6	$C_{25}H_{22}N_4O_4S$	474.14	265-267	69	63.28 (63.01)	4.67 (4.25)	11.81 (11.20)
A_7	$C_{24}H_{20}ClN_3O_2S$	449.10	230-233	72	64.06 (65.85)	4.48 (4.10)	9.34 (9.01)
A_8	$C_{24}H_{20}N_4O_4S$	460.50	234-238	65	62.60 (62.10)	4.38 (4.12)	12.17 (12.01)
A_9	$C_{24}H_{20}N_4O_4S$	460.50	210-215	65	62.60 (62.10)	4.38 (4.31)	12.17 (11.95)
A_{10}	$C_{24}H_{19}ClN_4O_3S$	478.09	185-190	71	60.19 (60.02)	4.00 (3.75)	11.70 (11.20)
A_{11}	$C_{24}H_{20}N_4O_4S$	460.12	240-242	62	62.60 (62.10)	4.38 (4.10)	12.17 (11.95)

Table 2. Antidepressant activity of the compounds in despair swim test on rats**.**

Compound code	Immobility time			% Immobility		
	1 h	5 h	24 h	1 h	5 h	24 h
A_1	141	148.5	157.5	81.97	81.36	80.76
A_2	148.5	153.5	156	86.33	84.10	80.00
A_3	143.5	149	153.5	83.43	81.64	78.71
A_4	150	156	158	87.20	85.47	81.02
A_5	153.5	157.5	163.5	89.24	86.30	83.84
A_6	140	143	145	81.39	78.35	74.35
A_7	143.5	146.5	157.5	83.43	80.27	80.76
A_8	140	150	159	81.39	82.19	81.58
A_9	153	161	160	88.95	88.21	82.05
A_{10}	146	153.5	153.5	84.88	84.10	78.71
A_{11}	158.5	162.5	162.5	92.15	89.40	83.33
Control	172	182.5	195	100	100	100
Imipramine (std.)	136.5	150.5	154.5	79.41	82.49	79.26

Table 3. Equations generated between log (% Inh) and descriptors

Sr. No.	Equation	N	S	R	r^2	r^2_{cv}	F
series (A_1-A_9 and B_1-B_9)	Y = - 0.218*X3- 1.576 X2 - 13.218	11	0.364	0.835	0.697	0.487	13.816

where Y = log (% Inh) ; X1: ClogP; X2 = VAMP HOMO (whole molecule); X3 = dipole moment Z component (whole molecule); X4 = inertia moment 2 length (whole molecule)

Significance of the terms **–**N= No. of molecules; s = standard error --- less is better**;** r = correlation coefficient – higher is better > 0.7 **;** r^2cv = cross validated r^2 - higher is better > 0.5, F value = higher is better**;** observed and predicted data and graphs are presented in Table 4 and Graph I for the series

Table 4. Observed and predicted log (% Inh) value data for 11 compounds

Comp. No.	Observed Value	Predicted Value	Residual Value	Residual Variance
A_1	1.842983	1.83868347	-0.0043	0.0057
A_2	1.821448	1.825048019	0.0036	0.0078
A_3	1.828724	1.819724327	-0.009	0.0049
A_4	1.722634	1.718733923	-0.0039	0.0198
A_5	1.835881	1.840780732	0.0049	0.0073
A_6	1.828724	1.836424327	0.0077	0.0044
A_7	1.821448	1.807048019	-0.0144	0.0347
A_8	1.835881	1.829880732	-0.006	0.0184
A_9	1.828724	1.830024327	0.0013	0.0092
A_{10}	1.828724	1.836424327	0.0077	0.0044
A_{11}	1.828724	1.830024327	0.0013	0.0092

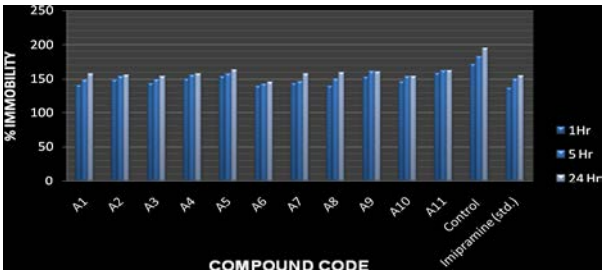


Fig.1. Antidepressant effects of schiff base derivatives of benzothiazepine compared with the control group, imipramine used as standard compound.

Fig. 2. Antidepressant activity (Forced Swim Test in Rat) of the synthesized compounds

CONCLUSION

We investigated the importance of functional group substitutions in the structural framework of the compounds for their antidepressant activity. All compounds showed significant antidepressant activity at a dose of 25 mg/kg. The compounds A_3 and A_6 showed better activity. Finally, the encouraging result of the antidepressant activity displayed by these compounds may be of interest for further structural modifications to the lead compound and for next level studies in the hope of finding a new potent antidepressant prescription.

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QSAR-ИЗСЛЕДВАНЕ, СИНТЕЗА И АНТИ-ДЕПРЕСАНТНО ИЗСЛЕДВАНЕ НА НЯКОИ НОВИ ПРОИЗВОДНИ НА SCHIFF‘ОВИ БАЗИ С БЕНЗОТИАЗЕПИН

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(Резюме)

В тази работа се съобщава за синтезирането, охарактеризирането и оценяването на фармакологичната активност на някои нови производни на Schiff‘ови бази с бензотиазепин. Чистотата на синтезираните съединения е потвърдена с помощта на тънкослойна хроматография. Точките на топене са определени по капилярния метод. Съединенията са охарактеризирани с IR, NMR и мас-спектроскопия. Анти-депресантната активност на всички синтезирани съединения е оценена с теста „despair swim“ върху *Sprague Dawley*-плъхове. Като контрола е използван имипрамин. Всички синтезирани съединения показват анти-депресантна активност. QSAR-изследване на описаните съединения е извършено с използването на софтуер TSAR 3.3 и резултатите са задоволителни. Получените резултати ще са полезни за бъдещи изследвания.