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Research Article

SYNTHESIS, CHARACTERIZATION AND PHARMACOLOGICAL EVALUATION OF STRUCTURALLY RELATED COMPOUNDS OF DIBENZOXEPIN AND DIBENZOTHIEPIN

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ABSTRACT
This study was designed to synthesize, characterize and to evaluate the pharmacological activity of Dibenzoxepin and Dibenzothiepin derivatives. Totally three compounds, two Dibenzoxepin derivatives and one Dibenzothiepin derivative were synthesized by conventional method. Purity of the synthesized compounds was ascertained by TLC and melting point determination by open capillary tube method and they were characterized by IR and NMR spectroscopic methods. Antidepressant activity of all the synthesized compounds was evaluated by despair swim test by using Swiss albino mice. Standard drug Imipramine was used as the control. In the results of the spectral study, all the compounds showed characteristic peak in IR and NMR spectroscopy. In the despair swim test, all the synthesized derivatives showed antidepressant activity. Among them one compound (PC158) showed significant antidepressant activity comparing with control drug imipramine. These results are useful for the further investigation in the future.
Keywords: Antidepressant activity, Dibenzoxepin and Dibenzothiepin derivatives, Despair swim test, Swiss albino mice

INTRODUCTION

Depression is a serious medical issue characterized by a variety of debilitating symptoms, such as persistent sadness and anxiety, chronic fatigue, feelings of worthlessness, disturbances in cognitive functioning and thoughts and attempts of suicide[1]. Depression has been determined to be the leading cause of disability and the 4th leading contributor to the global burden of disease and is characterized by relapse, recurrence and chronicity[2]. Research on major depression has confirmed that it is caused by an array of bio psychosocial and lifestyle factors. Diet, exercise and sleep are three such influences that play a significant mediating role in the development, progression and treatment of this condition[3]. Antidepressants are the drugs used to treat depression thereby elevates mood and modifies the behavior. Half a century ago, antidepressants were discovered by serendipity[4]. The development of the first effective antidepressants in the late 1950s marked a turning point in the treatment of depressive illness. In the 1957 the monoamine oxidase inhibitor (MAOI) iproniazid was discovered by chance, while searching for new anti tuberculoses drugs. One year later the tricyclic antidepressant (TCA) imipramine was introduced, having been developed originally as an antipsychotic[5]. Thus the early antidepressant medications such as TCAs and MAOIs are effective because they enhance either noradrenergic or serotonergic mechanisms or both[6]. A number of other drugs were subsequently added to these two groups of antidepressants, which dominated the field for the next three decades. In the 1970s and 1980s some new antidepressants such as mianserin, zimeldine, nomifensine, maprotiline and trazodone were introduced. However it was the antidepressants developed in the late 1980s and the 1990s more specifically the selective serotonin reuptake inhibitors (SSRIs) which seriously threatened the position of the TCAs as the first choice drugs in the treatment of depression[5]. Treatment of depression is gaining importance in recent years. Current treatments for depression either fail to produce complete recovery or induce unwanted side effects. So there is still a large unmet clinical need[7-9]. The main aims in the development of new antidepressants were greater efficacy, absence of side effects, lack of toxicity in over dose and earlier onset of action[5]. Elaborate research work has been carried out in the past and continuing in the present to synthesize new compounds to meet this depression. The development of antidepressants requires simple rodent behavioral tests for initial screening before undertaking more complex preclinical tests and clinical evaluation. The forced swim test (behavioral despair test) and tail suspension test in the mouse are 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. Both the tests are base on the same principle: measurement of the duration of immobility when rodents are exposed to an inescapable situation. The majority of clinically used antidepressants decrease the duration of immobility. Testing of new substances in the behavioral despair and tail suspension tests allows a simple assessment of their potential antidepressant activity by the measurement of their effect on immobility[7]. Several tricyclic compounds and their derivatives containing oxygen and sulphur atom have been effectively synthesized and used as antidepressant. The synthetic route available for these compounds is quite complicated and many reactions involved, go in facile manner and having lesser percentage yield. So to improve the reaction conditions and make these synthetic routes practically more viable to suite the industrial requirements, the alternative routes and modifications at various stages of these preparations become imperative. With this view the present work was designed to establish modification in synthesis of oxygen and sulphur containing tricyclic system and their antidepressant activity was evaluated by the forced swim test to make the synthetic route more appropriate and viable for needs of the industry. It is an attempt to provide a direction for further research.

MATERIALS AND METHODS

Three derivatives were proposed for the synthesis. They are

1) {3-[6H- Dibenzo[b,e]- (11E)- ylidene]- propyl]-methyl-amine. (PC 156)
2) {3-[6H- Dibenzo [be] oxepin- (11Z)- ylidene]propyl}-dimethyl amine. (PC 157)
3) Dimethyl-{3-[11H-10-Thia-dibenzo[a,d]cyclohepten-(5E)-ylidene]propylamine. (PC158)

The proposed derivatives were synthesized by conventional method.

Synthesis of PC 156

Synthesis of [3-(10,11-dihydro-dibenz[b, e] oxepin-5-yl)-propyl]-methyl-carbamic acid ethyl ester

100 g of Doxepin hydrochloride was mixed with 200 ml of water and the pH was adjusted to 9 by using sodium carbonate. It was extracted with 200 ml of benzene and the benzene layer was separated by using separated by using separating funnel. 50 g of potassium carbonate was added to separate benzene. This mixture was refluxed with 200 ml of ethylchloroformate for 2 h. Then reaction mixture was concentrated and the benzene was removed by distillation and condensation and the residue was collected and dried.

Synthesis of 11- methyl amino propyl (E) ylidene- 6,11-dihydro-dibenzo[b,e]oxepin

210 g of potassium hydroxide was mixed with 70 ml of water and 200 ml of N-butyl alcohol. This mixture was refluxed with 70 g of product obtained in synthetic step-1 for 2 h. Then 400 ml of water and toluene was added with continuous stirring. The toluene layer was evaporated and the residue was collected and dried.

Synthesis of {3-[6H- Dibenzo [b, e]- (11E)- ylidene]-propyl]-methyl-amine

52 g of product obtained in synthetic step-2 was mixed with 300 ml of acetone and 10 g of charcoal. This mixture was filtered after slight warming. The filtrate was acidified with hydrochloric acid to pH 2. This mixture was cooled and the resultant product was isolated by filtration and dried. Yield and melting point of product obtained were determined. A single spot on the TLC plate established the purity of the compound. The solvent system used was acetone : chloroform (1:1)

Synthesis of PC 157

22 g Doxipen hydrochloride was mixed with 100 ml of xylene. 6 ml hydrochloric acid was added in drop wise and refluxed at 110^{o}C for 10 h. The reaction mixture was concentrated and the xylene was removed by distillation. Then 100 ml toluene was added and continues the distillation. Finally 120 ml acetone was added to the reaction mixture. The solid product thus separated out was filtered and dried. Yield, melting point and R_f value of the product were recorded.

Synthesis of PC 158

20 g Dothipen hydrochloride was mixed with 150 ml acetic acid. 19.5 ml hydrogen peroxide (30 %) was added drop wise with stirring and kept in the room temperature over night. After that 500 ml water was added to reaction mixture and the pH was adjusted to 9 by using sodium carbonate. 500 ml methyl dichlorane was added to reaction mixture with stirring. The reaction mixture was concentrated and methyl dichlorane was removed by distillation. The residue was mixed with 120 ml acetone and the pH was adjusted to 2 by using hydrochloric acid. The precipitate thus formed was separated and dried. Yield, melting point and R_f value of the product were recorded.

Characterization of synthesized compound by spectral study

IR Spectrum

IR spectra were recorded by using KBr pellets in the range of 4000 – 500 cm^{-1} on Jasco FTIR Model 4100 Type A to elucidate the structure of the compounds.

NMR Spectrum

Bruker spectrospin-200 NMR spectrophotometer was used. $CDCl_3$ and DMSO are used as solvents.

Evaluation of antidepressant activity

Antidepressant activity of all the synthesized compounds was evaluated by despair swim test. Healthy young adult male Swiss albino mice weighing 25-30 g were used for the experiment. They were housed in standard environmental conditions like ambient temperature (25^{o}C ± 1^{o}C) relative humidity (55 ± 5 %) and 12 hour light / dark cycle. Animals had free access to standard pellet diet and water *ad libitum*. Swiss albino mice were divided in to five group of six each. One group served as normal control which received food and water only. One group served as standard control which received the standard drug imipramine. Remaining each group received the test agents PC–156, PC-157, and PC-158 individually. The standard drug and the test agents at the dose of 10 ml/kg were administered orally one hour prior to the testing. All the mice were individually forced to swim inside a vertical Plexiglas cylinder with 40 cm height and 18 cm diameter filled with water in the temperature of 24^{o}C ± 1^{o}C up to 15 cm height and the behavior of mice (duration of immobility) were observed.

RESULTS

In the present study, totally three compounds, two Dibenzoxepin derivatives and one Dibenzothiepin derivative were synthesized. All the synthesized compounds are in white powder form. Molecular formula, weight and yield of all the synthesized compounds were shown in Table 1. Purity of the synthesized compounds was ascertained by TLC and melting point determination by open capillary tube method (Table 2) and they were characterized by IR and NMR spectroscopic methods. All the compounds showed characteristic peak in IR and NMR spectroscopic studies (Graph 1-5). All the synthesized compounds were subjected to antidepressant activity study on Swiss albino mice by despair swim test. Imipramine was used as standard control. The animals show more stable levels of immobility during the last four minutes of the session. The results showed that all the compounds showed antidepressant activity. Among them one compound (PC158) showed significant antidepressant activity comparing with standard control imipramine (Table 3).

Table 1: Molecular formula, weight and yield of the synthesized compounds

No	Compound Code	Molecular formula	Molecular Weight	Yield
1	PC 156	$C_{18}H_{19}NO$	264.37	65 %
2	PC 157	$C_{19}H_{21}NO.HCl$	279.39	90 %
3	PC 158	$C_{19}H_{21}SON$	295.45	60 %

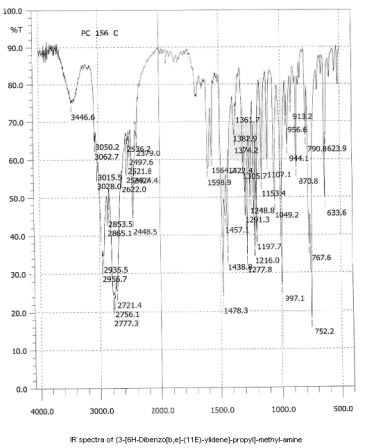
Table 2: Characterization data of synthesized compounds

No	Compound Code	R_f Value	Melting point (^{0}c)
1	PC156	0.76	232-234
2	PC157	0.69	248-250
3	PC158	0.78	262-265

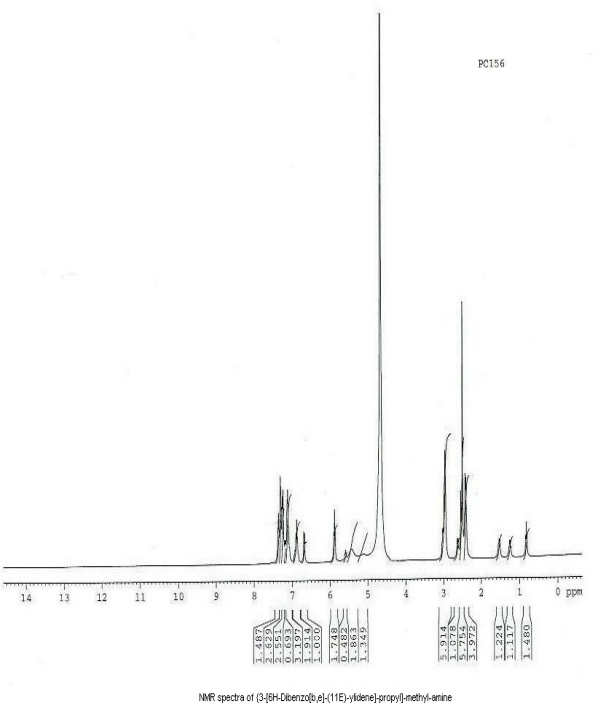
Table 3: Antidepressant activity of synthesized compounds in despair swim test on Swiss albino mice

Group	Immobility time (Mean)
Control	144.33 ± 8.819
PC156	115.16 ± 6.118*
PC157	30.5 ± 7.482**
PC158	22.33 ± 1.054**
Standard control	16.08 ± 1.781**

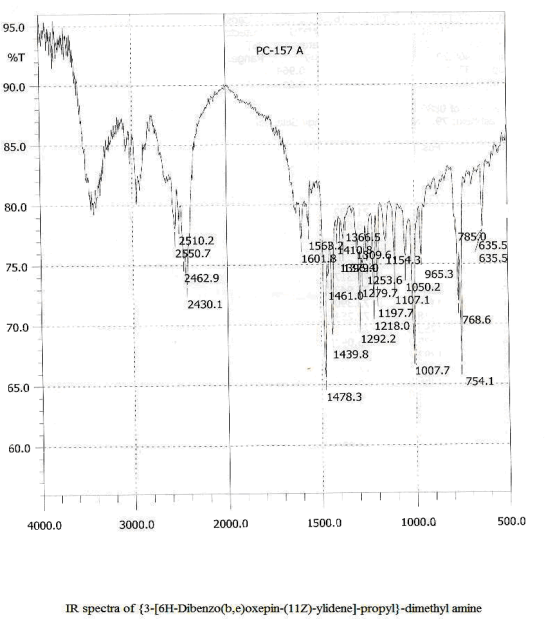
All values mean ± SEM, n = 6, *p < 0.05, **p < 0.01 compare to control



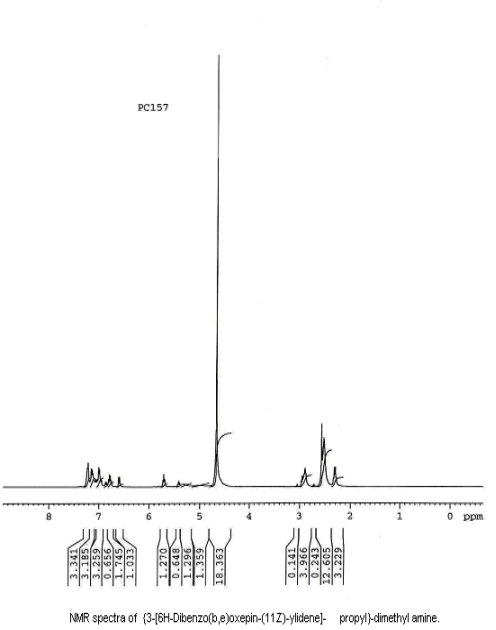
Graph 1: IR report for the compound PC 156



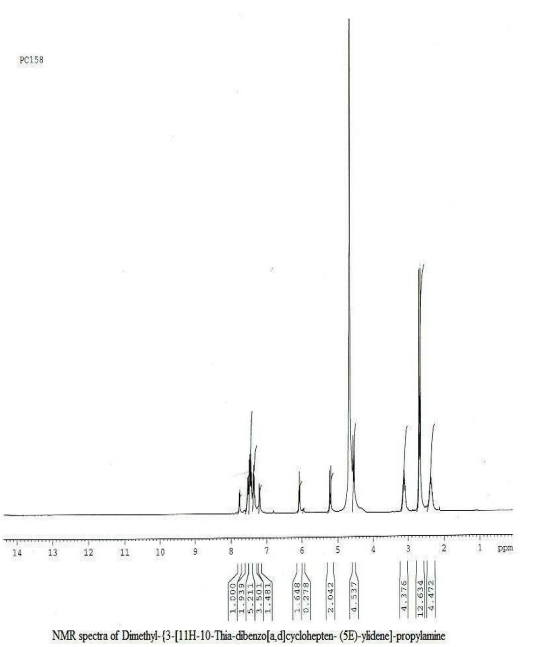
Graph 2: NMR report for the compound PC 156



Graph 3: IR report for the compound PC 157



Graph 4: NMR report for the compound PC 157



Graph 5: NMR report for the compound PC 158

DISCUSSION

Several tricyclic compounds and their derivatives containing oxygen and sulphur atom have been effectively synthesized and used as antidepressants. The synthetic route available for these compounds is quite complicated and many reactions involved. So that the alternative routes and modifications at various stages of these preparations are necessary. With this view the present study was designed. In the present study, totally three compounds, two Dibenzoxepin derivatives and one Dibenzothiepin derivative were synthesized by conventional method. The synthesized compounds were characterized by TLC, melting point determination, IR and NMR spectroscopic evaluations. Despair swim test on Swiss albino mice was employed for the evaluation of the pharmacological activity of synthesized compounds with imipramine as the standard control. In the despair swim test, all the synthesized compounds showed anti depressant activity. Among them one compound (PC158) showed significant antidepressant activity comparing with control drug imipramine. These results suggest that these compounds needs further study.

CONCLUSION

Depression still remains a common devastating disorder worldwide. Treatment of depression is gaining importance in recent years. Elaborate research work has been carried out in the past and continuing in the present to synthesize new compounds to meet this depression. In the present study two Dibenzoxepin derivatives and one Dibenzothiepin derivative were synthesized by conventional method and characterized by TLC, melting point determination, IR and NMR spectroscopic evaluations. In the evaluation of antidepressant activity, one of the synthesized compounds (PC158) showed significant activity comparing with standard control drug imipramine. From these studies, it is clear that further works needed to be done in the future for the development of clinically useful chemotherapeutic agents.

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REFERENCES

1. Ray M Merrill, Arielle A Sloan. Associations between the use of antidepressants and other medications. Open Journal of Depression 2014; 3(1): 24-31. http://dx.doi.org/10.4236/ojd.2014.31007
2. Joanna L Iddon, Lee Grant. Behavioral and cognitive treatment interventions in depression: An analysis of the evidence base. Open Journal of Depression 2013; 2(2): 11-15. http://dx.doi.org/10.4236/ojd.2013.22003
3. Adrian L Lopresti, Sean D Hood, Peter D Drummond. A review of lifestyle factors that contribute to important pathways associated with major depression: Diet, sleep and exercise. Journal of Affective Disorders 2013; 148(1): 12-27. http://dx.doi.org/10.1016/j.jad.2013.01.014
4. Benoit Petit – Demouliere, Franck Chenu, Michel Bourin. Forced swimming test in mice: A review of antidepressant activity. Psychopharmacology 2005; 177: 245-255. http://dx.doi.org/10.1007/s00213-004-2048-7
5. Eleni Palazidou. Development of new antidepressants. Advances in Psychiatric treatment 1997; 3: 46-51. http://dx.doi.org/10.1192/apt.3.1.46
6. Pal Pacher, Eva Kohegyi, Valeria Kecskemeti, Susanna Furst. Current trends in the development of new antidepressants. Current Medicinal Chemistry 2001; 8(2): 89-100. http://dx.doi.org/10.2174/0929867013373796
7. Vincent Castagne, Paul Moser, Sylvain Roux, Roger D Porsolt. Rodent models of depression: Forced swim and tail suspension behavioral despair tests in rats and mice. Current Protocols in Pharmacology 2010; 49: 5.8.1-5.8.14.
8. Baghai TC, Volz HP, Moller HJ. Drug treatment of depression in the 2000s: An overview of achievements in the last 10 years and future possibilities. World J. Biol. Psychiatry 2006; 7: 198-222. http://dx.doi.org/10.1080/15622970601003973
9. Slattery DA, Hudson AL, Nutt DJ. Invited review: The evolution of antidepressant mechanisms. Fundam. Clin. Pharmacol. 2004; 18: 1-21. http://dx.doi.org/10.1111/j.1472-8206.2004.00195.x

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