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Antidepressant-like Activity of 2-Pyrazoline Derivatives

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ÖZET

Antidepresan benzeri etkili 2-pirazolin türevleri

Amaç: Yaygın, kronik ve tekrarlama riski olan psikiyatrik bir hastalık olarak depresyon, farklı sistemleri etkileyebilen semptomlar bütünüyle karakterize edilir. Patogenezinde rol oynayan çok farklı sistemlerin olması ve tedaviye verilen yanıtta görülen farklar, ilaç tedavisiyle tam bir iyileşme sağlanmasını engelleyerek yeni tedavi seçeneklerinin keşfedilmesi için yapılan çalışmaları hızlandırmaktadır. Daha önce birçok araştırmada pirazolin türevlerinin antidepresan ajan olarak tedavi potansiyeline sahip oldukları gösterilmiştir. Bu çalışmada ise bir seri yeni 2-pirazolin türevlerinin antidepresan benzeri etki profillerinin aydınlatılması amaçlanmıştır.

Yöntem: Antidepresan benzeri aktivite Balb/C farelerde kuyruktan asma testi ve bu testte etkili olduğu tespit edilen maddeler için zorunlu yüzme testi kullanılarak değerlendirilmiştir. Her iki testte de antidepresan benzeri etkinin göstergesi, her bir hayvan için toplam hareketsiz kalma süresi olarak kabul edilmiştir.

Bulgular: 3d ve 3e kodlu test bileşiklerinin antidepresan benzeri etkili olduğu belirlenmiş ve uygulanan her iki testte de referans ilaç imipramin grubunda gözlendiği gibi hareketsiz kalma sürelerinde kısalma gözlenmiştir. Ayrıca bileşikler farelerde lokomotor aktiviteyi etkilememiştir.

Sonuç: Sonuçlarımız, 2-pirazolin türevi olan 3d ve 3e'nin depresyon tedavisinde yeni aday bileşiklerin tasarımı için potansiyel test maddeleri olduğunu göstermektedir.

Anahtar sözcükler: Antidepresan benzeri aktivite, 2-pirazolin türevleri, zorunlu yüzme testi, kuyruktan asma testi

ABSTRACT

Antidepressant-like activity of 2-pyrazoline derivatives

Objective: Depression is a common chronic recurrent psychiatric disorder, characterised by clusters of symptoms affecting many different systems. Due to complexity of the pathogenesis and differences in response to treatment, current therapies are incapable of providing an exact recovery, leading to attempts to investigate new treatment options. In many studies, it is shown that pyrazoline derivatives have the therapeutic potential as antidepressant agents. In this study, we aimed to investigate the antidepressant-like profile of a series of new 2-pyrazoline derivatives.

Methods: Antidepressant-like activity was evaluated by using tail suspension test, which was followed by forced swim test for those compounds found effective in tail suspension test in Balb/c mice. The behavioural parameter observed in both tests was immobility period, which is an indicative of antidepressant-like effect.

Results: Test compounds 3d and 3e were effective and a significant reduction in immobility time was observed when compared to results of imipramin, as the reference drug. Additionally, these two compounds did not alter the locomotor activity in mice.

Conclusion: Our results indicate that two 2-pyrazoline derivatives, 3d and 3e, are potential compounds for use in designing of new candidates for the treatment of depression.

Key words: Antidepressant-like activity, 2-pyrazoline derivatives, forced swim test, tail suspension test

INTRODUCTION

The World Health Organisation (WHO) estimates that 151 million people worldwide suffer from depression and every year approximately 844 thousand people die by suicide, which is the most severe consequence of uncontrolled depression (1). Additionally, WHO predicts that depression will be the second leading cause of death by 2020 due to cardiovascular and stress-related complications, notwithstanding that it is a psychiatric condition (2). Many authorities define depression as a symptomatically, psychologically and biologically heterogenous and as the most prevalent mental disorder. The disorder was characterized by apathy, loss of energy, retardation of thinking and activity, as well as profound feelings of gloominess, despair and suicidal ideation (3,4).

Medications such as tricyclic antidepressants (TCAs), selective serotonin reuptake inhibitors (SSRIs), monoamine

oxidase inhibitors (MAOIs), specific serotonin-norepinephrine reuptake inhibitors (SNRIs), 5-HT2 receptor antagonists, and other heterocyclics are clinically employed for drug therapy. However, these drugs can impose a variety of side-effects including sedation, apathy, fatigue, sleep disturbance, cognitive impairment, and sexual dysfunction, and so forth, in addition to their inability to provide an exact recovery due to the complex pathogenesis of the disorder and differences in response to treatment. Hence, there remains a pressing need for new effective and better-tolerated antidepressants (5,6).

The development of synthetic heterocyclic compounds as antidepressants progressed considerably during the past decade. 2-Pyrazolines represent an important class of heterocycles due to their highly pronounced biological and pharmacological activities (7-11). Earlier studies on some 1,3,5-triphenyl- 2-pyrazolines, 3-(2''-hydroxy naphthalene-1''-yl)-1,5-diphenyl-2-pyrazolines, 1-thiocarbamoyl-3,5-diphenyl-2-pyrazolines and bicyclic pyrazolines revealed monoamine oxidase inhibitory activity in behavioural despair test (12-16). Furthermore, many analogues were found to be highly active inhibitory agents for both monoamine oxidase A and B (MAO-A and MAO-B) isoforms (17).

As part of our continuous efforts in this area, a series of some pyrazoline derivatives were synthesized to investigate their potential antidepressant-like activities. Antidepressant-like activity of 2-pyrazoline analogues has been evaluated by tail suspension test (TST) and forced swim test (FST) in mice.

MATERIALS AND METHODS

Chemistry

Synthesis of Test Compounds

The intermediated chalcones (1a-e) were prepared by reacting equimolar aldehyde and ketone in presence of a base by conventional Claisen-Schmidt condensation. 3,5-disubstituted-4,5-dihydro-1H-pyrazole-1-carbothioamides (2a-e) were synthesized by refluxing compounds 1a-e and thiosemicarbazide in the presence of alkaline medium and similiarly, N,3,5-trisubstituted-4,5-dihydro-1H-pyrazole-1-carboxamides (3a-e) were synthesized by refluxing selected chalcones with N-(4-chlorophenyl)semicarbazide in alkaline medium. Physicochemical and spectroscopic characterization of the 2-pyrazoline derivatives 2a-e and 3a-e have been previously described (18). The purities of the synthesized compounds were checked by reversed phase HPLC (Chromasil C18 3.6 x150 mm column using acetonitrile and water (50:50 v/v) as the eluent) and elemental analysis. All compounds showed a single and sharp peak with a retention time of 4.129- 5.690 min and also elemental analysis results were in 0.3%. Chemical structure of compounds 2a-e and 3a-e are shown in Figure 1.

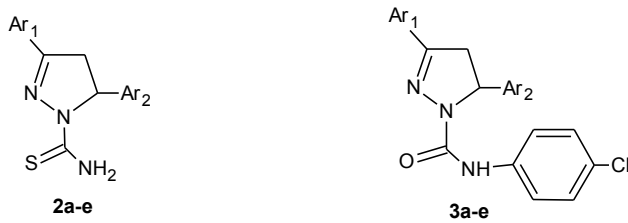

Figure 1: Chemical structure of compounds **2a-e** and **3a**

Ar1: Phenyl, Ar2: 2,6-Dichlorophenyl (a), Ar1: 4-Methylsulfonylphenyl, Ar2: 2,6-Dichlorophenyl (b), Thiophen-2-yl, Ar2: 2,6-Dichlorophenyl (c), Ar1: 5-Bromothiophen-2-yl, Ar2: 2,6-Dichlorophenyl (d), Ar1: 5-Chlorothiophen-2-yl, Ar2: 2,6-Dichlorophenyl (e)

Evaluation of Antidepressant-like Activity

The antidepressant-like activity of the new chemicals were first determined by using TST. Compounds found effective in TST were reevaluated in FST (19, 20). In both tests, male and female adult Balb/c mice weighing 25-30 g were used. The animals were housed in colongy cages, under standard laboratory conditions, with free access to food and tap water. Room temperature and relative humidity were maintained at 22 ± 1 °C and 60%, respectively. A 12 h (8 am./8 pm.) light-dark cycle was used. All testing was conducted in the light phase of the day. After the adaption period of 2 days, experimental groups were chosen randomly. Each mouse was used only once. Mice were divided into groups as control, receiving saline, imipramine, receiving imipramine (15 mg/kg, i.p.) and groups for test compounds (n=8). Test compounds were applied 30 min before the experiment, as a single dose of 50 mg/kg, intraperitoneally.

Tail Suspension Test

Mice were suspended on the metal rod stand 50-75 cm above the table top by the adhesive tape placed approximately 1 cm from the tip of the tail to measure the duration of immobility. Immobility time was recorded during 6-min period. Animal was considered to be immobile when it did not show any movement of body and hanged passively. A decrease in the immobility period was considered as the indicator of the antidepressant-like activity.

Forced Swim Test

Compounds found effective in TST were reevaluated in FST. 30 min after the application of drugs, mice were immediately placed in a cylinder (30 cm high, 12 cm in diameter) filled with 20 cm of water that was meticulously maintained at 25°C±1°C. Mice were forced to swim for 6 min. They initially struggled to escape from the water, but eventually adopted a posture of immobility in which they made only movements necessary to keep their heads above water. A decrease in immobility time was considered as an indicator of antidepressant-like activity. After 6 min, the animals were removed from the water, dried, and placed in a warmed enclosure for 30 min. The cylinders were emptied and cleaned between each animal.

Statistical Analysis

Results from the tests are presented as mean ± SD. Data were analyzed by Kruskal Wallis test followed by the Dunn's multiple comparison test, using GraphPad Prism 5. Statistical significance was set as P<0,05.

RESULTS

Test Compounds

In our research to synthesize the antidepressant active 2-pyrazolines, a total of 10 compounds were synthesized (Figure 1). The purities of the synthesized compounds were checked by reversed phase HPLC and elemental analysis. The structures of the compounds were supported by the spectral data achieved from UV, IR, ^{1}H-NMR and mass spectroscopy, which were in agreement with the proposed structures (18).

Tail Suspension Test

In TST, most of the tested compounds showed no activity (Figure 2). Among the tested compounds, 3-(5-bromothiophen-2-yl)-N-(4-chlorophenyl)-5-(2,6-dichlorophenyl)-4,5-dihydro-1H-pyrazole-1-carboxamide (3d) ($p<0.01$) and N-(4-chlorophenyl)-5-(2,6-dichlorophenyl)-3-(5-chlorothiophen-2-yl)-4,5-dihydro-1H-pyrazole-1-carboxamide (3e) ($p<0.001$) were found nearly as active as imipramine ($p<0.001$) (Figure 3). These two molecules did not give similar results in FST (Figure 4).

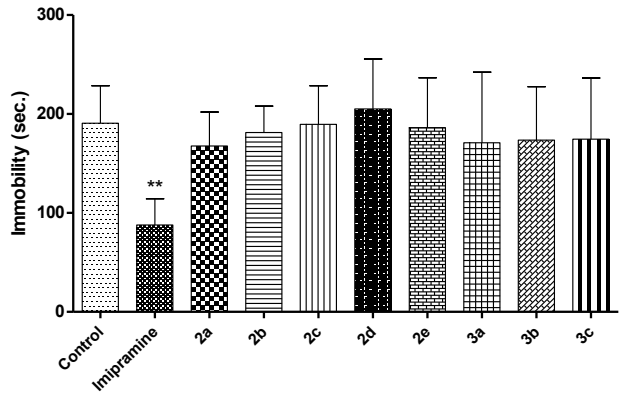

Figure 2: Antidepressant-like effects of 2-pyrazoline derivatives in TST. Data are presented as mean±SD (n=8) and **p<0,01 compared to control group.

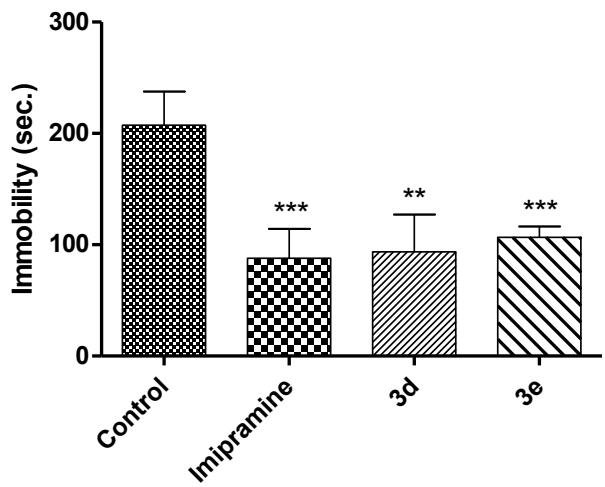

Figure 3: Results of active 2-pyrazoline derivative test compounds in TST Data are presented as mean±SD (n=8)and **p<0,01, ***p<0,001 compared to control group.

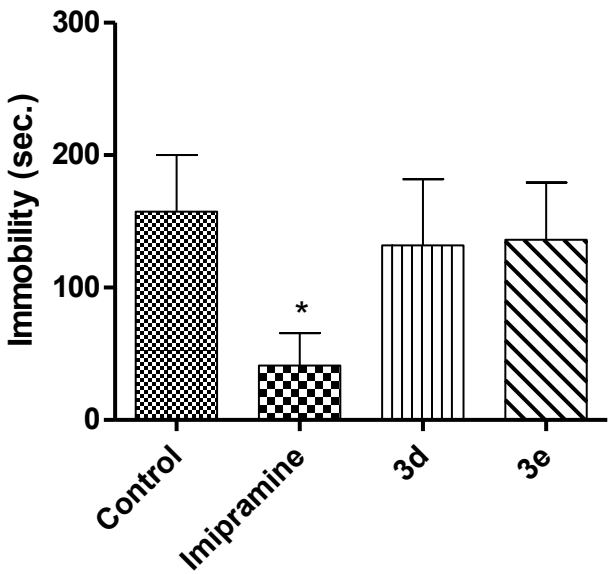

Figure 4: Antidepressant-like effects of 2-pyrazoline derivative test compounds in FST Data are presented as mean±SD (n=8) and *p<0,05 compared to control group.

Forced Swim Test

In FST, compounds 3d and 3e, already tested in TST and found as active, did not give statistically significant results, when compared with the results of the imipramine group ($p<0.05$). However, a decrease in immobility time was detected, when compared with results of the control group.

DISCUSSION

Taking efficacy, effectiveness, safety, side effects, and cost into account, available antidepressant are not satisfactory, while the incidence of depression in the society continuously increases. Therefore, there is still a large unmet clinical need and an immediate necessity of alternative medication. The development of heterocyclic compounds such as pyrazoline derivatives as potent antidepressants is progressing during the past decade (21).

Many animal models are available for assessing the stress-precipitated depressive behaviour. The two most common behavioural models for studying the antidepressant-like activity are the forced swim test and tail suspension test, which were used in our study (22). These tests are quite sensitive and relatively specific to all major classes of antidepressant drugs. We chose to perform TST first and determined active compounds to be reevalutated in FST. By doing so, we aimed to decrease the amount of test compunds and the number of animals used.

The newly synthesized compounds were evaluated for their antidepressant-like activity by two models with well-established predictive values: tail suspension test and forced swim tests. A mild antidepressant-like activity of 3d and 3e may be reached after evaluating results of the tail suspension test, as providing a marked decrease in immobility time of mice. This effect of two compounds was not encouraged by forced swim test, in which decrease in immobility time also reflects the antidepressant activity. This may be due to various reasons.

In a study, discussing effects of ketamine on negative symptoms of schizophrenia, FST and TST were used. As a result, in the acute treatment group, increased immobility was observed in TST, but not in FST and in the chronic treatment group the same result was detected in FST (23). It is speculated that, TST is more sensitive than FST to rapid neurochemical changes. Therefore, our results may overlap the findings of the aforementioned study.

The results of the forced swim test and tail suspension test indicate the potency of test compounds 3d and 3e as they showed a decrease in the immobility time. Drugs that alter the general motor activity of the animals may give false positive/negative results. From the photoactometer test for a period of 5 min for each mouse, it is demonstrated that the test compounds did not effect the locomotor activity in mice. And hence, it is probable that the antidepressant-like effect of the test compounds is specific and not due to the motor stimulation. The exact mechanism by which these compounds is not understood however, the activity of the compounds 3d and 3e may be supported due to the presence of carboxamide moiety and thiophen ring in their structure. Test compounds 3d and 3e might also be active due to the presence of electron withdrawing group of chloro and bromo on thiophen ring . The activity of the compounds might be worth for further investigation and elucidation.

CONCLUSION

In conclusion, a series of 2-pyrazoline derivatives were synthesized and screened for their antidepressant-like activity. The antidepressant-like activity screening

indicated that among the tested compounds, 3d and 3e showed noteworthy activity in TST test. Based on the activity results, it appears that halogen atoms on the thiophen ring have made good contribution to the antidepressant-like activity.

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