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Research Article

Synthesis and Evaluation for Anxiolytic Activity of Few Substituted Dihydropyrazolyl-thiazoline-4-one Derivatives

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ABSTRACT

Anxiolytic drugs are used for the treatment of anxiety disorders and their related psychological and physical symptoms. Today's increased anxiolytic drug resistance has resulted in serious health issues. Thus, there is an ever-increasing demand for design and synthesis of newer drugs for treatment. The present work reports the synthesis of some derivatives of pyrazolyl thiazolino-4-one viz. 2-[3-(furan-2-yl)-5-substituted phenyl-4,5-dihydro-1*H*-pyrazole-1-yl]-1,3-thiazole-4(5*H*)-ones. Six derivatives have been synthesized and the chemical structures were confirmed by infrared spectroscopy (IR), proton nuclear magnetic resonance (H^1-NMR) and carbon-13 nuclear magnetic resonance (^{13}C-NMR). All the compounds were subjected for toxicity studies and then evaluated for their anxiolytic activity using elevated plus maze apparatus on rats. LD_{50} was found to be 98.11 mg/Kg. An increase in percentage of time spent and number of entries in open arm of the plus maze signals a good potential as minimizing anxiety in rats. All the results were statistically tested by one way ANOVA followed by Dunnett's test. Compound 2; 2-[3-(furan-2-yl)-5-(4-dimethylamino-phenyl)- 4,5-dihydro-1*H*-pyrazol-1-yl]-1,3-thiazol-4(5*H*)-one and compound 5; 2-[3-(furan-2-yl)-5-(2-chlorophenyl)-4,5-dihydro-1*H*-pyrazol-1-yl]-1,3-thiazol-4(5*H*)-one have shown percentage preference to open arm as 15.11 and 14.17 seconds and average time spent in open arm as 45.33 and 42.50 seconds, respectively and thus resulted in significant anxiolytic effect as compared to control. These compounds can serve as potential leads for the development of newer therapeutic agents for the treatment of anxiety.

Introduction

Anxiety is a feeling of fear, dread, and unease are all symptoms of anxiety. It can make you sweat, feel restless and tight, and cause your heart to race. It could be a typical stress response. Antianxiety medications are commonly referred to as anxiolytics. A large number of effective anti-anxiety medications are now available. Anxiolytic drugs are used for the treatment of anxiety disorders and their related psychological and physical symptoms. It is an emotion that is characterized by an unpleasant state of inner turmoil and it includes subjectively unpleasant feelings of dread over anticipated events. It is often accompanied by nervous behavior such as pacing back and forth, somatic complaints, and rumination.[1]

Anxiolytics may cause drowsiness or dizziness. Other side effects include lowered blood pressure, slowed breathing, and problems with memory. Long-term use can make side effects worse. With today's increase, anxiolytic drug resistance have resulted in serious health issues[2,3] As a result, novel anxiolytic drugs must be designed and synthesized quickly. Thiazolines are a group of isomeric 5- membered heterocyclic compound, their derivatives are more common and some are bioactive. Some of the approved drugs are dasatinib (anticancer), ritonavir (anti-HIV), nizatidine (anti-ulcer), and fentiazac (anti-inflammatory), among several medicines. Natural products containing both or one of the thiazoline and thiazole moieties include apratoxins, firefly luciferin, dolastatin E, mirabazole, tantazoles, piscibactin, etc. show

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a wide range of biological activities such as anticancer, antimicrobial, antimalarial, anti-tuberculosis, neurotoxic, and many other useful properties There are reports of design of few derivatives of pyrazolyl-triazolinones.[4]

Synthesis of a series of pyrazolyl thiazolinone derivatives and their biological activities as potential EGFR and HER-2 kinase inhibitors has been reported, among them, compound 2-(5-(4 bromophenyl)-3-p-tolyl-4,5-dihydro-1H-pyrazol-1-yl)-thiazol-4(SH)-one displayed the most potent inhibitory activity.[5] The synthesis, biological evaluation, new pyrazoline bearing 4(3*H*)-quinazolinone as structural determinants of MAO-A and MAO-B selectivity has also been reported.[6] In search of novel and effective antitumor agents, pyrazoline-substituted pyrrolidine-2,5-dione hybrids were designed, synthesized and evaluated *in-silico, in-vitro* and *in-vivo* for anticancer efficacy. The excellent antiproliferative activity toward MCF7 (IC_{50}=0.78 ± 0.01 μM), HT29 (IC_{50}=0.92 ± 0.15 μM) and K562 (IC_{50}=47.25 ± 1.24 μM) cell lines, prompted us to further investigate the antitumor effects of the best compound 1-(2-(3-(4-fluorophenyl)-5-(p-tolyl)-4,5-dihydro-1H-pyrazol-1-yl)-2-oxoethyl)-pyrrolidine-2,5-dione. It was found to disrupt the growth phases with increased cell population in $G1/G_0$ phase and decreased cell population in G_2/M phase.[7]

Synthesis of a series of 1,3,5-trisubstituted-2-pyrazolines *via* Claisen Schmidt condensation, followed by heterocyclization with hydrazine hydrate and substitution of N^1 hydrogen of 2-pyrazoline nucleus with 4-chlorobenzenesulfonylchloride was reported by applying conventional and green chemistry approaches. The compounds were evaluated for anti-anxiety activity. The compound, 1-(p-chlorobenzensulfonyl)-3-(p-hydroxy phenyl)-5-(p-chloro phenyl)-2-pyrazoline showed excellent activity.[8]

Synthesis and evaluation for antidepressant and anxiolytic activities of some new 3-(4-fluorophenyl)-5-aryl-N-substituted-4,5-dihydro-1*H*-pyrazole-1-carbothioamide derivatives were reported. The compounds were evaluated in vitro for their monoamine oxidase A and B inhibitory activity and selectivity. The derivatives substituted by halogen on the fifth position of pyrazole ring, inhibited monoamine oxidase-A enzyme with a high selectivity index. On the other hand, compounds substituted with 2-naphthyl inhibited monoamine oxidase-B enzyme with a moderate selectivity index. Docking studies were done to highlight the interactions of the most active derivative with the active site of monoamine oxidase-A. In addition, in vivo antidepressant and anxiolytic activities of the compounds having selective monoamine oxidase-A inhibitory effects, were investigated by using Porsolt forced swimming and elevated plus-maze tests, respectively. 3-(4-fluorophenyl)-5-(4-chloro-phenyl)-N-allyl-4,5-dihydro-1*H*-pyrazole-1-carbothio-amide has antidepressant activity, 3-(4-fluorophenyl)-5-(4-chlorophenyl)-N-methyl-4,5-dihydro-1*H*-pyrazole-1-carbothioamide and 3-(4-fluoro -phenyl)-5-(4-bromophenyl)-N-ethyl-4,5-dihydro-1*H*-pyrazole-1-carbothioamide have anxiolytic activity.[9]

Design and synthesis of a novel series of 1, 3-thiazole linked 1,2,3-triazole derivatives were reported. Molecular docking was studied to illustrate the binding interactions of target molecules with $GABA_A$ receptor. The *in-vivo* activity result revealed that some of the compounds possessed statistically significant therapeutic efficacy. Anti-anxiety screening on mice indicated that all the target compounds (5 mg/kg) exhibited a certain extent of an anxiolytic effect by increasing time spent on open arms and the percentage of open arm entries as compared to the controlled group. More importantly, among the newly synthesized two compounds have shown strong anti-anxiety against mice. Molecular docking simulations were employed to find out the important binding modes responsible for the anti-anxiety activity, thus supporting their effective anti-anxiety efficacy.[10]

The present investigation reports the synthesis, and characterization of novel derivatives of pyrazolyl-thiazoline-4-one derivatives and the evaluation of their anxiolytic activity using an elevated plus maze.

Materials And Methods

All the reagents and solvents were purchased from commercially available sources and used without further purification. Melting points were recorded in open capillaries using ELICO melting point apparatus and are uncorrected. The progress of the reaction was monitored by thin layer chromatography on silica gel-coated glass plate and products were purified through recrystallization and purity of the compounds was ascertained by single spot-on TLC sheet in solvent system A- chloroform: methanol (0.9:0.1) and the spots were located by iodine. The FTIR spectra were recorded on FTIR Shimadzu affinity-1 infrared spectrophotometer using KBr as a diluent. NMR spectra were recorded on Bruker Avance II 400 spectrometer and TMS as an internal standard at SAIF, Punjab University, Chandigarh.

General Procedure

Step-1: Synthesis of 1-(furan-2-yl)-3-substituted phenyl-prop-2-en-1-one

An equimolar mixture of the variously substituted aromatic aldehyde and 2-acetyl furan in 25 mL of ethanol was allowed to stir for 30 minutes at 10°C. The 1-mL of sodium hydroxide solution was added dropwise to the reaction mixture. The reaction mixture was then allowed to stir at room temperature for 6–8 hours. The reaction mixture was poured into crushed ice and solid thus obtained was filtered and dried. The crude product was recrystallized from ethanol.[11]

Step-2: Synthesis of 3-(furan-2-yl)-5-substituted phenyl-4,5-dihydro-1H-pyrazole-1-carbothioamide

An equimolar mixture of 1-(furan-2-yl)-3-substituted phenyl prop-2-en-1-one, thiosemicarbazide and potassium

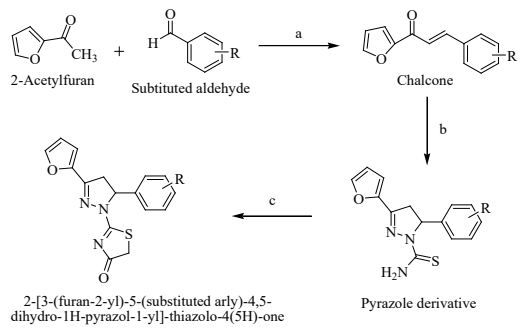

Fig. 1: Scheme for Synthesis of 2-[3-(furan-2-yl)-5-(substituted aryl)-4,5-dihydro-1*H*-pyrazol-1-yl]- thiazol-4(5*H*)-one.
a: NaOH, stir at 10oC, 6–8 hours; b: Ethanol, reflux, 14 hours ; c: Stir 80oC, 8–10 hours.

hydroxide was refluxed in ethanol for 14 hours. Cooled to room temperature and poured into crushed ice and solid thus obtained was filtered and dried. The crude product was recrystallized from ethanol.

Step-3 Synthesis of 2-[3-(furan-2-yl)-5-substituted phenyl-4,5-dihydro-1H-pyrazole-1-yl]-1,3-thiazole-4(5H)-one

A mixture of 3-(furan-2-yl)-5-substituted phenyl-4,5-dihydro-1*H*-pyrazole-1-carbothioamide. (1 mmol), bromoacetic acid (1.2 mmol) was dissolved in acetic acid (20 mL). The mixture was stirred 80°C for 8–10 hours. Cooled to room temperature and poured into crushed ice and solid thus obtained was filtered and dried. The crude product was recrystallized from ethanol see Fig. 1.

Acute Toxicity Studies

OECD guidelines (no. 425) were followed for acute toxicity studies in mice to obtain median lethal dose (LD_{50}). Each animal was observed for signs of toxicity as well as for mortality in the first 30 minutes after dosing and then occasionally for further 4 hours and daily thereafter for a period of 14 days. The number of mice dying during 48 hours period was recorded.

Evaluation of Anxiolytic Activity using Elevated Plus Maze

The rats weighing within 180–200 gm were selected and divided into groups of six animals each. One group was vehicle control (1% tween-80 in saline), one group was for studying the protective effects of diazepam (Standard; dose: 2 mg/kg). Other groups were of the test compounds. The rats were treated with diazepam or the test compounds 60 minutes before evaluation in the maze. In the test each rat will be individually examined in 5 minutes sessions in this apparatus. Each rat was placed in the central platform facing one open arm. The numbers of entries into open and closed arms and the time spent in the, respective arms were recorded during a 5 minutes period. The percentage of time spent in the open arms was calculated for each rat.[12]

Results And Discussion

Chemistry

Here in the synthesis six derivatives of 2-[3-(furan-2-yl)-5-(substituted aryl)-4,5-dihydro-1*H*-pyrazol-1-yl]- thiazol-4(5*H*)-one has been reported which are expected to have anxiolytic activity. The synthesis of novel compound comprised of three steps; firstly, the chalcones viz. 1-(furan-2-yl)-3-substituted phenyl-prop-2-en-1-ones were prepared, then chalcones were condensed with thiosemicarbazide to obtain 3-(furan-2-yl)-5-substituted phenyl-4,5-dihydro-1*H*-pyrazole-1-carbothioamide derivatives and then on the third step, the pyrazoline derivative were condensed with bromoacetic acid to obtain the final compounds. The compounds were obtained in moderate to good yields ranging from 67–78%. The Infrared spectrum of the newly synthesized pyrazolyl-thiazolinone derivatives shows a characteristic absorption band within 1593–1630 cm^{-1} for C=N (Imine). The C-N band also appear at within 1151–1284 cm^{-1}. The ^{1}H-NMR showed the -CH_2 protons of the pyrazoline ring resonated as a pair of doublets of doublets at 2.90–3.38 δ ppm, and that of thiazolinone at 4.12–4.37 δ ppm, respectively. In ^{13}C-NMR, it was also observed that the characteristic chemical shift values appear at δ 38-39 ppm for thiazolinone rings carbons CH_2 and at 46–45 ppm, 59–60 ppm, 150–152 ppm for pyrazoline ring carbons CH, CH_2 and C=N, respectively.

(1) 2-[3-(furan-2-yl)-5-(2-phenylethylene)-4,5-dihydro-1H-pyrazole-1-yl]-1,3-thiazole-4(5H)-one

Yellowish brown solid in 72%, mp: 58-60°C, R_f :0.58 (Solvent system A), IR V_{max} (KBr cm^{-1}): 1616 (C=N), 1473 (C=C), 1265 (C-N), 1718 (C=O), 1350 (C-O), ^{1}H-NMR (400MHz, δ ppm, DMSO-d_6): 3.04-3.10 (2H,dd,-CH_2 pyrazole), 4.18-4.32 (2H,d,-CH_2 thiazolinone), 5.23 (1H,ddd,-CH), 6.44-6.46 (3H, dd, aromatic, furyl), 6.51 (1H,d,CH), 6.89 (1H,dd, CH), 7.03-7.41 (5H, m, aromatic). ^{13}C-NMR (δ_c ppm, DMSO-d_6): 38, 45, 56, 112, 127, 130, 134, 140, 151,152, 178, 187

(2) 2-[3-(furan-2-yl)-5-(4-dimethylaminophenyl)-4,5-dihydro-1H-pyrazol-1-yl]- thiazol-4(5H)-one

Brown solid in 67%, mp: 66-68°C; IR (KBr cm^{-1}): 1630 (C=N), 1446 (C=C); 1236 (C-N), 1705 (C=O), 3037 (C-H), 1046 (C-O). ^{1}H-NMR (400MHz, δ ppm, DMSO-d_6): 2.71 (6H, s CH_3), 2.90 (2H, dd, -CH_2 pyrazole), 4.19-4.22 (2H, d, -CH_2, thiazolinone), 5.61 (1H, dd, -CH), 6.34 (1H, dd,), 6.51-6.61 (3H, m, aromatic, furyl), 6.80-6.99 (4H, m, aromatic). ^{13}C-NMR (δ_c ppm, DMSO-d_6): 39, 45, 63, 112, 126, 139, 143, 150,152, 177, 186

(3) 2-[3-(furan-2-yl)-5-(3-nitrophenyl)-4,5-dihydro-1H-pyrazol-1yl]- thiazol-4(5H)-one

Yellowish white solid in 78% mp: 54-56°C, IR V_{max} (KBr cm^{-1}): 1593 (C=N), 1338 (C=C), 1157 (C-N), 1504 (N=O),

Table 1: Anxiolytic effect of some synthesized pyrazolyl thiazolin-4-one derivatives in rats using Elevated plus maze apparatus.

Compound	*%Preference to open arm*	*Open arm No. of entries (mean ± SEM)*	*Average time spent (sec) (mean ± SEM)*
1	7.18*	3.40 ± 0.13*	24.10 ± 0.61*
2	15.11**	4.16 ± 0.30**	45.33 ± 0.66**
3	6.83	2.33 ± 0.21	20.50 ± 0.76
4	9.82*	3.66 ± 0.38*	31.15 ± 0.24*
5	14.17**	4.33 ± 0.42**	42.50 ± 0.76**
6	6.01	2.09 ± 0.22	15.19 ± 0.29
Control (1% Tween 80 in normal saline)	5.33	2 ± 0.25	16 ± 0.57
Diazepam 2mg/Kg	19.50	4.83 ± 0.47	58.50 ± 0.76

N=6, in each group; *:$p < 0.05$; **:$p < 0.001$: S: significant; One Way ANOVA followed Dunnett's test. Value expressed as Mean ± SEM

1311 (C-O); ^{1}H-NMR (400 MHz, δ ppm, DMSO-d_6): 3.14-3.27 (2H, dd, CH_2 pyrazole), 3.87 (1H, dd, pyrazole), 4.14 (2H, d, thiazolinone), 6.85-7.10 (3H aromatic, furyl), 7.66-8.14 (4H, m, Aromatic). ^{13}C-NMR (δ_c ppm, DMSO-d_6): 39, 46, 63, 111, 112, 119, 123, 127, 138, 143, 152, 176, 188

(4) *2-[3-(furan-2-yl)-5-(4-methoxyphenyl)-4,5-dihydro-1H-pyrazol-1-yl]- thiazol-4(5H)-one:*

Yellowish brown solid in 67%; mp:64-66°C; IR V_{max} (KBr cm^{-1}): 1151 (C-N), 1458 (C=C) 1625 (C=N), 1710 (C=O), 3045 (C-H), 1046 (C-O), ^{1}H-NMR (400MHz, δ ppm, DMSO-d_6): 2.96 (1H, dd), 3.04-3.10 (2H, d, CH_2 pyrazole), 3.27 (1H, dd), 3.69 (3H, s, -OCH_3), 5.61 (1H, dd), 6.34 (1H, dd), 6.82-6.99 (4H, m, phenyl). ^{13}C-NMR (δ_c ppm, DMSO-d_6): 40, 45, 55, 64, 111, 114, 127, 138, 143, 152, 159, 176, 187

(5) *2-[3-(furan-2-yl)-5-(2-chlorophenyl)- 4,5-dihydro-1H-pyrazol-1-yl]-1,3-thiazol-4(5H)-one.*

Off white solid in 75%; mp: 50-52°C, IR V_{max} (KBr cm^{-1}): 1284 (C-N), 1423 (C=C), 756 (C-Cl), 1284(C-O). ^{1}H-NMR (400MHz, δ ppm, DMSO-d_6): 3.30-3.38 (2H, dd, -CH_2, pyrazole), 3.92 (1H, dd, -CH pyrazole), 4.22-4.37 (2H, d, thiazolinone), 7.22-7.67 (4H phenyl), 7.97-8.17 (3H furyl). ^{13}C-NMR (δ_c ppm, DMSO-d_6): 38, 46, 60, 111, 117, 128, 133, 136, 144, 151, 154, 178, 188

(6) *2-[3-(furan-2-yl)-5-(2-hydroxyphenyl)-4,5-dihydro-1H-pyrazol-1-yl]- thiazol-4(5H)-one.*

Brown solid in 70%; mp:68-70°C; IR V_{max} (KBr cm^{-1}): 1199 (C-N), 1423 (C=C), 1506 (N=C), 3371 (O-H). ^{1}H-NMR (400MHz, δ ppm, DMSO-d_6): 3.10 (1H, dd, -OH), 3.34 (1H, dd), 4.12-4.20 (2H, d, thiazolinone) 5.69 (1H, dd), 6.34-6.45 (3H, m, furyl), 6.87-7.11 (4H, m, phenyl). ^{13}C-NMR (δ_c ppm, DMSO-d_6): 39, 46, 59, 112, 117, 127, 129, 144, 152, 154, 177, 188

Pharmacological Evaluation

Determination of LD_{50} (Acute Toxicity Study)

LD_{50} was calculated by using the software AOT425StatPgm. LD_{50} was calculated as 98.11 mg/kg. The actual dose taken for evaluation of activity of the synthesized compounds was 10 mg/kg (Approx. 1/10th that of LD_{50})

Antxiolytic Activity Study

The elevated plus maze test on rats is a feasible animal model to evaluate the compound for potential as anxiolytic activity. The elevated plus maze test is used to assess anxiety-related behavior in rodent models of CNS disorders. It consists of a "+"-shaped maze elevated above the floor with two oppositely positioned closed arms, two oppositely positioned open arms, and a center area. Rats freely explore the maze, their behavior is recorded by means of a video camera mounted above the maze and analyzed using a video tracking system. The preference for being in open arms over closed arms (expressed as either as a percentage of entries and/or a percentage of time spent in the open arms) is calculated to measure anxiety-like behavior. This test can be used to phenotype strains of transgenic mice and to screen for the putative anxiolytic compound. An increase in the percentage of time spent and number of entries in open arm of the plus maze signals a good potential as minimizing anxiety in rats. Rats were observed for 5 minutes duration after 60 minutes of administration of the compounds. The observations were compared with control. Observations were recorded in Table 1. It was observed that the number of entries in open arm was 2.09 to 4.33; average time spent in open arm was 15.19 to 45.33 seconds and percentage preference to open arm was 6.01 to 15.11 compared to 2, 6 seconds and 5.33, respectively for control, 1% Tween-80 in normal saline.

Conclusion

The synthesis of Dihydropyrazolyl-thiazolin-4-one derivatives was comprised of three steps; starting from various chalcones derived from 2-aetyl furan and substituted aromatic aldehydes. The structures of the compounds were confirmed by Instrumental analysis. During the acute toxicity studies, the LD_{50} was found to be 98.11 mg/Kg. A 10 mg/Kg dose was administered during the evaluation of anxiolytic activity using elevated plus maze. Increase in percentage of time spent and number of entries in open arm of the plus maze signals a good potential as minimizing anxiety in rats. All the results were statistically tested by one way ANOVA

followed by Dunnett's test. Compound 2; 2-[3-(furan-2-yl)-5-(4-dimethylamino-phenyl)- 4,5-dihydro-1*H*-pyrazol-1-yl]-1,3-thiazol-4(5*H*)-one and compound 5; 2-[3-(furan-2-yl)-5-(2-chlorophenyl)-4,5-dihydro-1*H*-pyrazol-1-yl]-1,3-thiazol-4(5*H*)-one has shown percentage preference to open arm as 15.11 and 14.17 seconds and average time spent in open arm as 45.33 and 42.50 seconds, respectively and thus resulted in significant anxiolytic effect as compared to control. These compounds can serve as potential leads for development of newer therapeutic agents for the treatment of anxiety.

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