Asian Journal of Pharmaceutical and Health Sciences
www.ajphs.com

Design, Synthesis of Novel Quinoxaline Derivatives & Their Antinociceptive Activity

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ARTICLE HISTORY

Received 10-Sep-2011

Accepted 25-Oct-20

Available online 10-Feb-2012

Keywords:

Quinoxaline, anilines, aldehydes, antinociceptive Activity

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ABSTRACT

Quinoxaline derivatives constitute an important class of heterocycles in drug discovery and it acts as important structural motif for the discovery of biologically efficient compounds. A series of novel quinoxaline derivatives of Schiff bases were synthesized and evaluated by antinociceptive activity. Initiation of reaction by reacting orthophenylene diamine and á-ketoglutaric acid and a intermediate is obtained. Further refluxion of intermediate yields the formation of 3-(3-Oxo-3,4dihydro-quinoxalin-2-yl)- propionic acid methyl ester which was on refluxion with substituted aromatic amines results a formation of Schiff base derivatives of aromatic amines. Promoting the scheme by further refluxion of and hydrazine hydrate yields the 3-(3-Oxo-3,4dihydro-quinoxalin-2-yl)- propionic acid hydrazide which was condensed with different aldehydes resulted a formation of Schiff base derivatives of aldehyde. The structures of the synthesized compounds were confirmed by spectral data and elemental analysis. The synthetic compounds were screened for the analgesic activities.The compounds DIA-2 is the most potent and DIA-5, ACP-3 showed significant analgesic activity (central) comparable with pethidine. The compound ACP-4 were found to be most active and DIA-3,ACP-1,ACP-3 also shows considerable protection against writhing test (peripheral) comparable with diclofenac sodium. Quinoxaline nucleus due to its high degree of diversity has been proven useful for the development of newer pain relieving agents having improved potency and lesser toxicity.

INTRODUCTION

Pain is an unpleasant sensation, with a large subjective components associated with depression [1] & feeling of hopelessness. Chronic persistent pain impact negatively on quality of life, affects several aspects of health and well-being including relationships, cognitive abilities and the capacity to work. Analgesics are drugs that selectively relieve pain by acting on the central nervous system or on a peripheral pain mechanism, without significantly altering consciousness. A wide range of different analgesic drugs is available for use in man but it is convenient to consider them in two broad groups, opioid and non opioid analgesics [2]. Opioids include drugs which basically act on central nervous system & alter the pain perception of an individual. This class is represented by morphine [3] and its analogues. The centrally acting agents are generally the most potent analgesics. But they are reserved for chronic severe pain only as they cause addiction. Non opioids are mainly synthetic in nature as well as less potent as compared with narcotic analgesics. They are used for mild to moderate pain. Non opioid analgesics are commonly known as non steroidal anti-inflammatory drugs (NSAIDs).

NSAIDs excerts its action by blocking the metabolism of arachidonic acid through the enzyme cyclo-oxygenase (COX) and lowering the production of prostaglandins e.g., PGE_2, which sensitize nociceptors at nerve fibre terminal. Three isoforms of COX have been identified,COX-1 & COX-2 and recently discovered COX-3 that is splice variant of COX-1. COX-3 inhibition by analgesics/antipyretic drugs through which acetaminophen decreases pain and fever [4]. Various therapies available for chronic pain prevention [5] and currently available analgesics such as opiates and NSAIDs are also present but they are not much potent as they are associated with adverse effects. Long-term clinical usage of NSAIDs is associated with significant side effects of gastrointestinal lesions, bleeding, and nephrotoxicity.

In view of these findings organic compounds bearing quinoxaline nuclei were found to possess potent analgesic activity. This biological importance prompted us to synthesize some new heterocyclic derivatives having quinoxaline nucleus in order to investigate analgesic activities as well as for the development of more potent compounds that selectively inhibit COX-2, thus reducing the inflammatory response.

Experimental Protocol Chemistry

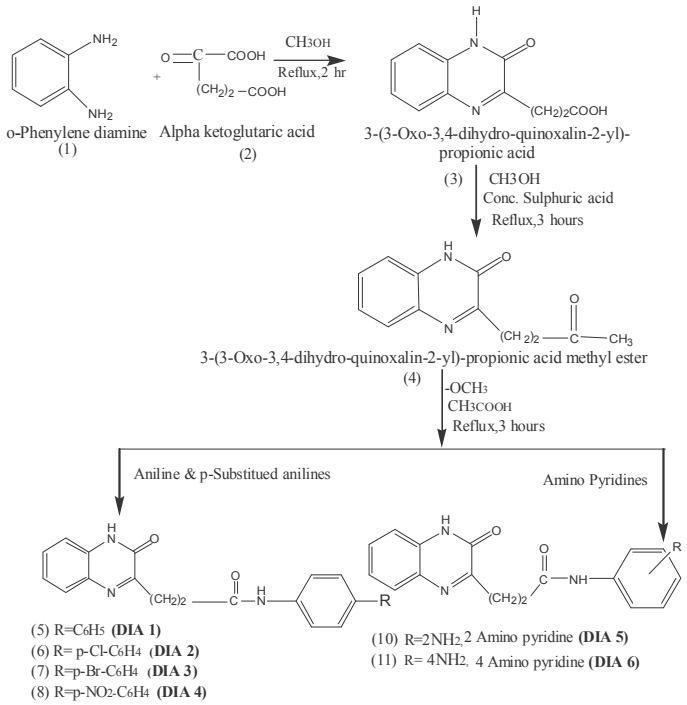
(A) Synthesis of Schiff Bases of Aromatic Amines

The target compounds were synthesized as outlined in scheme 1 and 2.Target compounds of scheme 1 were synthesized by taking equimolar quantities of orthophenylene diamine (1) and á-ketoglutaric acid (2) and dissolving both of them in methanol in a round bottom flask & refluxed for two hours. The reaction mixture was filtered and 3-(3-Oxo-3,4dihydro-quinoxalin-2-yl)-propionic acid(3) as a intermediate is obtained which was refluxed with methanol & conc. Sulphuric acid for three hours. The final Schiff base derivatives of aromatic amines such as anilines(5-8) and pyridines (9-10) were obtained by refluxing 3-(3-Oxo-3,4dihydro-quinoxalin-2-yl)-propionic acid methyl ester(4) with different p-Substituted aniline & 2 or 4-Amino pyridines such as aniline(5),p-Cl-aniline(6),p-Br-aniline(7),p-NO2-aniline(8),2-amino-pyridine(9),4-amino-pyridine(10) with glacial acetic acid for two hours in a round bottom flask.

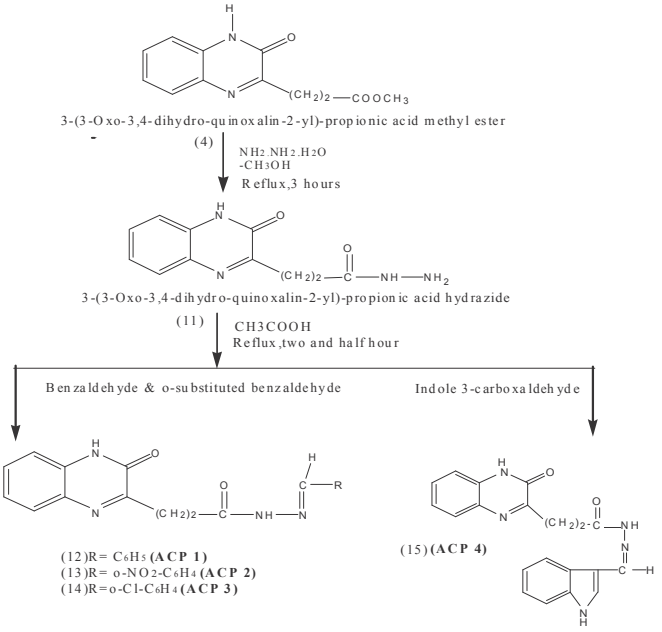
(B) Synthesis of Schiff Bases of Substitued Aldehyde Derivatives

For the synthesis of scheme 2 derivatives further refluxing 3-(3-Oxo-3, 4dihydro-quinoxalin-2-yl)-propionic acid methyl ester (4) with hydrazine hydrate resulted the formation of 3-(3-Oxo-3, 4dihydro-quinoxalin-2-yl)-propionic acid hydrazide(11) as an intermediate. Addition of different aldehydes and 3-(3-Oxo-3,4dihydro-quinoxalin-2-yl)-propionic acid hydrazide (11) in presence of acetic acid was refluxed for two and half hour with different aldehydes such as benzaldehyde(12),2-NO2-benzaldehyde(13),2-Cl-benzaldehyde(14),indole-3-carboxaldehyde(15) results a formation Schiff base derivatives of aldehydes.

The reaction progress for Scheme 1 & 2 were observed by TLC monitoring and final crude product was filtered, re-crystallized by benzene and characterized by their elemental & spectral analysis.



Scheme 1 : Synthesis of schiff bases of aromatic amines



Scheme 2: Synthesis of schiff bases of substitued aldehyde derivatives

METHODOLOGY

Melting points of the synthesized compounds were taken by open capillary method using the Thistle tube apparatus and are uncorrected. The homogeneity of the synthesized compounds was monitored by ascending thin layer chromatography (TLC) on silica gel G coated plates and visualized by using iodine vapours with different solvent systems.IR spectra were recorded on Thermo Electron Corporation, USA-Model-Avatar 370 FTIR by using potassium bromide pellets and the values are reported in $\tilde{o}_{max}$ cm^{-1}.^{1}H NMR spectrum of compounds was recorded on AV-500 using CDCL3 as a solvent and chemical shift(ä) is reported in parts per million downfield.

PHYSICAL CHARACTERIZATION AND SPECTRAL DATA

1. 3-(3-Oxo-3,4-dihydro-quinoxalin-2-yl)-N-phenyl-propionamide (DIA1)

Black,% Yield-60.31,m.p.- 84-87^{0}C, **IR (KBr)$\tilde{o}_{max}$ cm^{-1}-**3500(amide NH strech),1690(C=O str of amide),2890(C-H stretch),1340(C-N str of amine),1680(C=N str),1420(CH2 bend),1520(C=C Ar),690(out of plane bend Ar),**^{1}H NMR (300 MHZ, DMSO) ä (ppm)**-7.7-7.9(d,4H,Ar-H(Quinoxaline), 1.7 (s,2H,CH2), 2.3 (s,2H,CH2—C=O), 7.0-7.64 (d,5H,Ar-H), 8.0 (s,2H,NH),Anal. Calcd. for C17H15N3O2 (293.320):C-69.61, H-5.15, N-14.33,Found: C-69.58,H-5.14,N-14.30.

2. N-(4-Chloro-phenyl)-3-(3-oxo-3,4-dihydro-quinoxalin-2-yl)-propionamide (DIA2)

Dark brown,% Yield-91.42,m.p.- 200-202^{0}C,**IR (KBr)$\tilde{o}_{max}$ cm^{-1}**-3500(amide NH strech), 1640 (C=O str of amide),2850(C-H stretch),1000(C-N str of amine),1640(C=N str), 1500 (C=C Ar), 770(out of plane bend Ar),610(C-Cl), **^{1}H NMR (300 MHZ, DMSO) ä (ppm)**-7.0-7.8(d,4H,Ar-H(Quinoxaline), 1.7 (s,4H,CH2), 7.24 -7.58 (d,4H,Ar-H), 8.0(s,2H,NH), 2.3 (s,4H, CH2), Anal. Calcd. for C17H14ClN3O2 (327.765):C-62.30,H-4.31, N-12.82. Found:C-62.28,H-4.27,N-12.78

3. N-(4-Bromo-phenyl)-3-(3-oxo-3,4-dihydro-quinoxalin-2-yl)-propionamide (DIA3)

Brown,% Yield-51.25,m.p.-215-217^{0}C,**IR (KBr)õ$_{max}$ cm^{-1}-**3690(amide NH strech), 1623(C=O str of amide),2890(C-H stretch),1229(C-N str of amine),1680(C=N str),1558(C=C Ar), 800(out of plane bend Ar),660(C-Br),**^{1}H NMR (300 MHZ ,DMSO) ä (ppm)-**7.0-7.8 (d,4H,Ar-H(Quinoxaline), 1.8(s,2H,CH2), 7.41-7.53 (d,4H, Ar-H), 8.0(s,2H,NH), 2.3(s,2H, CH2),Anal. Calcd. for C17H14BrN3O2 (372.216):C-54.86,H-3.79,N-11.29,Found: C-54.85,H-3.75, N-11.26.

4. N-(4-Nitro-phenyl)-3-(3- oxo-3,4-dihydro-quinoxalin-2-yl)-propionamide (DIA4)

Light brown,% Yield-48.61,m.p.-210-212^{0}C,**IR (KBr)õ cm^{-1}-**3500(amide NH strech), 1630(C=O str of amide),2860(C-H stretch),1210(C-N str of amine),1480(CH2 bend), 1495(C=C Ar),680(out of plane bend Ar), 1530(asymmetric Ar NO_2 stretch), 1390 (symmetric NO_2 Stretch), **^{1}H NMR(300 MHZ, DMSO) ä (ppm)-**7.0-7.6(s,4H,Ar-H(Quinoxaline), 1.7 (s, 2H, CH2), 7.90-8.17 (d,4H,Ar-H), 8.0(d,2H,NH), 2.3(s,2H,CH2), Anal. Calcd. for C17H14N4O4 (338.317): C-60.35,H-4.17,N-16.56, Found: C-60.32, H-4.15,N-16.53.

5. 3-(3-Oxo-3,4-dihydro-quinoxalin-2-yl)-N-pyridin-2-yl-propionamide (DIA5)

Dark brown,%Yield-25.39,m.p.-165-167^{0}C,**IR (KBr)õ$_{max}$cm^{-1}-**3400(amide NH strech), 1690(C=O str of amide),2890(C-H stretch),1210(C-N str of amine),1670(C=N str),1500(C=C Ar), 770(out of plane bend Ar), **^{1}H NMR (300 MHZ, DMSO) ä (ppm)-**7.0-7.6(d,4H,Ar-H(Quinoxaline)7.18-8.32(d,4H,CH,2-pyridine), 1.6-2.2(s,4H,CH2), 8.0(d,2H,NH),Anal. Calcd. for C16H14N4O2 (299.308): C-63.50,H-4.79,N-19.04, Found: C-63.48,H-4.76,N-19.01.

6. 3-(3-Oxo-3,4-dihydro-quinoxalin-2-yl)-N-pyridin-4-yl-propionamide (DIA6)

Dark brown,% Yield-25.39,m.p.-70-72^{0}C,**IR (KBr)õ$_{max}$ cm^{-1}-**3450(amide NH strech), 1660(C=O str of amide),3000(C-H stretch), 1020(C-N str of amine),1640(C=N str),1410(CH2 bend), 1475(C=C Ar),760(out of plane bend Ar),**^{1}H NMR (300 MHZ, DMSO) ä(ppm)-**7.0-7.7 (d,4H,Ar-H(Quinoxaline), 7.69-8.54(s,4H,4-pyridine), 1.6(s,2H,CH2), 8.0(s,2H,NH),2.2 (s,2H,CH2),Anal. Calcd. for C16H14N4O2 (299.308):C-63.30, H-4.79, N-19.04,Found: C-63.26, H-4.76,N-19.02.

7. 3-(3-Oxo-3,4-dihydro-quinoxalin-2-yl)-propionic acid benzylidene-hydrazide (ACP1)

Light pink,% Yield-84.058,m.p.-190-192^{0}C,**IR (KBr)õ$_{max}$ cm^{-1}-**3470 (amide NH strech), 1700(C=O str of amide),3000(C-H stretch), 1020(C-N str of amine),1680(C=N str),1400(CH2 bend), 1600 (C=C Ar), 780(out of plane bend Ar),**^{1}H NMR (300 MHZ, DMSO)ä(ppm)-**7.0-7.6(d,4H,Ar-H(Quinoxaline), 8.0 (s,2H,NH), 8.1 (s,1H,benzylidenimin), 7.3-7.6(d,5H, benzylide-nimin), 1.6(s,2H,CH2), 2.2(s,2H,CH2),Anal. Calcd. for C18H16N4O2 (320.34): C-67.49, H-5.03, N-17.49, Found:C-67.48, H-5.01,N-17.46.

8. 3-(3-Oxo-3,4-dihydro-quinoxalin-2-yl)-propionic acid (2-nitro-benzylidene)-hydrazide (ACP2)

Light Yellow,% Yield-78.48,m.p.-165-167^{0}C ,**IR (KBr)õ$_{max}$ cm^{-1}-**3499 (amide NH), 1700 (C=O str of amide), 2900 & 3200 (C-H stretch), 1350(C-N str of amine),1680(C=N str), 1400(CH2 bend), 1600(C=C Ar), 900(out of plane bend Ar), 1520(asymmetric Ar NO_2 stretch),**^{1}H NMR (300 MHZ, DMSO) ä (ppm)-** 7.0-7.4 (d,4H,Ar-H(Quinoxaline), 1.6 (s,2H,CH2), 2.2 (s,2H,CH2—C=O), 7.6-8.2(d,4H,benzylidenmin),8.0 (s,2H,NH), 8.1(s,1H, benzylidenmin),Anal. Calcd. for C18H15N5O4 (365.343): C-59.18,H-4.14, N-19.17, Found: C-59.14, H-4.10, N-19.15.

9. 3-(3-Oxo-3,4-dihydro-quinoxalin-2-yl)-propionic acid (2-chloro-benzylidene)-hydrazide (ACP3)

Yellow,% Yield-56.57,m.p.-100-102^{0}C,**IR (KBr)õ$_{max}$ cm^{-1}-**3500 (amide NH strech), 1680 (C=O str of amide), 3100(C-H stretch), 1250(C-N str of amine),1660(C=N str), 1400(CH2 bend), 1600(C=C Ar), 680(out of plane bend Ar), 760(Ar-Cl), **^{1}H NMR (300 MHZ, DMSO) ä (ppm)-**7.0-7.6(d,4H,Ar-H (Quinoxaline), 8.1(s,1H,NH), 8.2 (s,1H,benzyli-denimin),7.2-7.6 (s,4H,benzylidenimin), 1.6(s,2H,CH2), 2.2 (s,2H, CH2—C=O), 9.0(s,1H,NH), Anal. Calcd. for C18H15ClN4O2 (354.790) C-60.94, H-4.26, N-15.79,Found: C-60.90,H-4.23, N-15.78

10. 3-(3-Oxo-3,4-dihydro-quinoxalin-2-yl)-propionic acid (1H-indol-,3-ylmethylene)-hydrazide (ACP4)

Black,% Yield-31.17,m.p.-98-100 ^{0}C ,**IR (KBr)õ$_{max}$ cm^{-1}-**3469(amide NH strech),1650(C=O str of amide),3000(C-H stretch), 1000(C-N str of amine),1630(C=N str),1400(CH2 bend), 1600(C=C Ar),880(out of plane bend Ar), **^{1}H NMR (300 MHZ, DMSO) ä (ppm) -**7.0-7.6(d,4H, Ar-H(Quinoxaline), 7.0(s,1H,NH(sec.Amide & hydrazide), 7.0 (d,1H,NH, hydrazide), 7.50(d,1H,1H,hydrazide), 7.0-7.7(d,5H,3-indole), 1.6 (s,2H,CH2), 2.2 (s,2H,CH2—C=O),11.0(1H,NH,3-indole), Anal. Calcd. for C18H15ClN4O2 (354.790): C-66.84,H-4.77,N-19.49, Found: C-66.83,H-4.74,N-19.46.

Pharmacological Screening Antinociceptive Activity

MATERIALS AND METHODS

Experimental Animals & Diets

The healthy Swiss albino mice of both sexes weighing 23-25 g were taken for the study. The animals were kept in large spacious hygienic cages during the course of experimental period. The animals had free access to standard commercial diet and water ad libitum and were kept in room maintained at 22±1^{0}C with 12h light dark cycle with a relative humidity of 55±5 % in a standard wire meshed plastic cages for 4 to 5 hours before starting out the pharmacological screening. All animal experimentations were carried out with the guidelines of Animal Ethics Committee.

Acute toxicity study

We studied an acute toxicity of a novel quinoxaline derivatives in adult swiss albino mice according to OECD guidelines. For acute toxicity study ,mice were divided into seven groups having five animals in each group and determination of acute toxicity through oral route.First group served as a control treated with canola oil at the dose of 10 ml/kg and the rest of animal from the group 2-7 were treated with the graded dose of 500,600,750,850,1000 and 1100 mg/ kg b.w. orally using gastric tube and then observed for 24 hrs for signs of acute toxicity like behavioural changes including death[6].The calculated LD50 was 375 mg/kgb.w.

The LD50 was calculated using the arithmetic method of Karber by using the following formula:

LD50 = Least dose that killed all the animals – Sum of (Dose difference × Mean dose) / No. of animals/group

Assay of Antinociceptive activity using hot-plate test (Central)

The experiment was carried out by using Eddy's hot plate apparatus, maintained at 55±0.5^{0}C. The mice were divided into 12 groups of 6 animals each. The reaction time of the mice to the thermal stimulus was the time interval between placing the animal in hot plate & when it licked its hind paw or jumped. The reaction time was measured prior to aqueous suspension of synthesized compounds and drug treatment (0 min.).Group 1 was kept as normal control. The aqueous suspension of synthesized compounds was administered subcutaneously (s.c.) to mice of groups 2-11 at dose of 25mg/kg. Mice of group 12(reference)

Table No.1: Centeral analgesic activity (hot plate method)

Compound Code	Dose (mg/kg)	0 Minute	30 Minute	60 Minute	90 Minute
Control	--------	3.38±0.208	3.70±0.261	3.70±0.104	7.55±0.288
DIA 1	25mg/kg	2.15±0.261	3.77±0.106*	6.18±0.105*	6.57±0.339**
DIA 2	25mg/kg	4.283±0.247	9.25 ±0.114*	9.38 ±0.125*	12.29±0.276*
DIA 3	25mg/kg	2.483±0.228	4.81±0.083*	5.75 ±0.112*	7.21 ±0.199**
DIA 4	25mg/kg	2.3±0.199	4.85±0.051**	5.98 ±0.115*	6.81 ±0.384**
DIA 5	25mg/kg	4.1 ±0.166	9.06±0.030*	9.15±0.120*	12.16 ±0.265*
DIA 6	25mg/kg	2.23±0.320	8.06±0.094*	6.26±0.104*	6.78±0.380**
ACP 1	25mg/kg	3.88 ±0.275	7.56±0.127*	7.95 ±0.109*	8.88±0.251***
ACP 2	25mg/kg	3.78 ±0.296	7.56 ±0.110*	7.78±0.11*	8.88±0.294***
ACP 3	25mg/kg	4.27 ±0.239	8.15±0.116*	9.08±0.139*	11.55±0.312*
ACP 4	25mg/kg	2.63±0.224	5.57±0.097*	6.15±0.121*	7.37 ±0.181**
Pethidine#	5 mg/kg	4.44±0.215	9.33 ±0.094*	11.50±0.126*	14.45±0.245*

#Standard = 5 mg/kg b.w.

Dose of test drug = 25mg/kg b.w.

Values represent the mean ± SEM (n=6) at 0,30,60,90 minutes.

Values significant at p>0.05* *, p<0.05* * * and p<0.01* (Dunnett's test) as compared with respective control

Table No.2: Percent analgesic activity (peripheral, writhing test)

CMPD. CODE	DOSE (mg/kg)	WRIIHING EPISODES IN 15 MINUTES (MEAN±SEM)	% PROTECTION
Control	_____	47.11±0.377	_____
DIA 1	20mg/kg	24.85 ± 0.162*	47.25
DIA 2	20mg/kg	33.53 ± 0.207*	28.82
DIA 3	20mg/kg	17.21 ± 0.251*	63.46
DIA 4	20mg/kg	42.27± 0.319*	10.28
DIA 5	20mg/kg	29.10 ± 0.359 *	38.22
DIA 6	20mg/kg	33.53± 0.207*	28.82
ACP 1	20mg/kg	21.98± 0.157 *	53.32
ACP 2	20mg/kg	24.70± 0.172 *	47.56
ACP 3	20mg/kg	18.31 ± 0.114 *	61.12
ACP 4	20mg/kg	15.28 ± 0.284 *	67.56
Diclofenac sodium	20mg/kg	12.533± 0.269 *	73.39

#Standard = 20mg/kg b.w.

Dose of test drug = 20mg/kg b.w.

Each value represents the mean ±SEM (n=6) after 15 minutes of writhing.

Significant levels p<0.01* as compared with respective control

were treated with pethidine [7] at a dose of 5mg/kg(s.c.). The reaction time was again measured at 30 minute and repeated at 60 and 90 minutes after treatment. To avoid tissue damage to the mice paws, cut off time for the response to the thermal stimulus was set at 60 second. The reaction time was calculated for each synthesized and drug treated groups shown in Table No.1.

Assay of Antinociceptive activity using acetic acid induced writhing response model (Peripheral)

The compounds were selected for investigating their analgesic activity in acetic acid induced writhing response in Swiss albino mice, following the method of collier et al. The first group which served as control received distilled water in appropriate volume intra-peritoneal (i.p.).The 2-11 group received the aqueous suspension of synthesized compounds i.p. at a dose of 20mg/kg .The last group received diclofenac sodium i.p [8]. In a dose of 20mg/kg .After 30 minute each mice was administered with 0.7% of an aqueous suspension of acetic acid (10 ml/kg) and the mice were then placed in a transparent boxes for observation. The number of writhes was counted from 15 minutes after acetic acid injection and number of writhes in each treated group was compared to that of a control group. The number of writhing was recorded and the percentage protection was calculated using the following ratio % protection = (control mean- treated mean/control mean) ×100 shown in Table No.2.

Stastical Analysis

Values for antinociceptive activity determined through mean increase in prolonged activity after drug administration ±SEM in terms of seconds. The data was statistically analyzed using the one-way ANOVA to determine whether synthesized derivatives of Schiff base were significantly different from those in the corresponding control groups & it is determined through implementation of student's t-test.Values of $p<0.05$ were considered non-significant, $p>0.05$ considered moderately significant & $p<0.01$ are showing significant response.

RESULTS AND DISCUSSION

The Schiff base derivatives of aromatic amines and aldehyde were screened for their analgesic activity using both central analgesic and peripheral analgesic assays.Table 1 for the evaluation of antinociceptive activity reveals the response of animal when they are in contact with thermal stimulus. The animal licks its hind or fore paw with in a second before tested drug administered. When test drug administered to animal, the time period of animal kept in the hot plate get increased with respect to control. Due to chloro group the lipophilicity of the compound is increased due to which compound DIA-2 is the most potent compound among all the compounds screened for analgesic activity.The compounds DIA-5,ACP-3 show significant value at $p<0.01$ when compared with reference drug i.e., Pethidine. Compound ACP-4 shows moderate activity & the compounds DIA-1, DIA-3, DIA-4 show lesser amount of activity.

Table No.2 shows writhing episodes in mice at 15 minutes & it represents the abdominal contraction in mice by administering acetic acid solution intra-peritoneally (i.p.).After administration of diclofenac sodium (standard drug) writhing rates are reduced. The maximum decrease in no. of writhing is 15.28writhing/15 minutes shown by mice taking synthesized compound ACP-4 with respect to control animal showing 47.11 writhing/15 minutes.The compound ACP-4 bearing indole nucleus is an analog of chemically active drug indomethacin was found to be most active at $p<0.01$ among all the screened compounds for peripheral analgesic activity. The compounds DIA-3, ACP-1, ACP-3 also shows optimum protection against writhing test & all are significant at $p<0.01$.Compound ACP-3 having an o-Cl group showed desirable protection because of structural resemblance with diclofenac sodium. The results demonstrate that the compound DIA-2 is a most active compound against central analgesic assays and the compound ACP-4 show highest activity against peripheral analgesic assays.

CONCLUSIONS

The results depicts that the compound DIA-2 was most potent compound for central analgesic assay due to presence of chloro group & compound ACP-4 exhibited highest activity against peripheral analgesic assays due to its structural analogy with indomethacin.The other active compounds such as DIA-2,DIA-5,ACP-3, ACP-1 carrying a aryl rings along with quinoxaline nucleus bearing optimum analgesic activity. Structurally all the synthesized compounds were very much similar with COX-1 inhibitory agents. In nutshell, the synthesis of novel quinoxaline derivatives through substitution by different groups results a potential quinoxaline nucleus that acts as a novel drug template for assembly of large number of biologically active derivatives that produces marked pain relief & also leads a generation of newer & active agents for the formation of newer potent analgesics.

ACKNOWLEDGEMENT

The authors would like to thank Dr. Satyawan Singh (Director), Saroj Institute of Technology and Management, Lucknow for his kind and good cooperation to complete research work.

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