Journal of Medical Sciences

ISSN 1682-4474

science alert

ANSInet
an open access publisher
http://ansinet.com

Research Paper

J. Med. Sci., 12 (3): 61-69
1st April, 2012
DOI: 10.3923/jms.2012.61.69

Synthesis, Characterization and Pharmacological Evaluation of Novel Schiff Bases of Imide Moiety

S. Sharma, A.D.K. Jain, A. Aggarwal and N.S. Gill

Imides are the biologically active compounds having different pharmacological activities such as analgesic, anti-inflammatory, anti-microbial, anti-depressant and anti-cancer etc. These compounds play an important role in medicinal chemistry in drug development and drug discovery. In this research novel Schiff bases of imides moiety have been synthesized which showed analgesic and anti-inflammatory activities. Novel Schiff base derivatives of imides moiety have been synthesized by multistep reaction. First step involves the reaction of phthalic anhydride with 4-amino benzaldehyde in the presence of dichloromethane which results in the formation of 4-(1,3-dioxoisoindolin-2-yl) benzaldehyde. Then, this compound on reaction with various derivatives of aniline in the presence of glacial acetic acid produced the desirable new Schiff bases. The structure of these compounds has been established by IR, ^{1}H-NMR studies and elemental analysis. The synthesized compounds were screened for their anti-inflammatory potential using carrageenan-induced rat paw edema model and analgesic activity by tail immersion and hot plate methods in mice at different concentrations i.e., 100, 200 and 300 mg kg^{-1}. The results showed that the Schiff bases of imide moiety possess significant therapeutic potential and can be used as analgesic and anti-inflammatory agents.

Key words: 4-(1,3-dioxoisoindolin-2-yl)benzaldehyde, phthalic anhydride, 4-amino benzaldehyde, Schiff bases, ethanolic solution of synthesized compound

JMS (ISSN 1682-4474) is an International, peer-reviewed scientific journal that publishes original article in experimental & clinical medicine and related disciplines such as molecular biology, biochemistry, genetics, biophysics, bio-and medical technology. JMS is issued eight times per year on paper and in electronic format.

For further information about this article or if you need reprints, please contact:

S. Sharma
Department of Pharmaceutical Chemistry,
Rayat Institute of Pharmacy,
Punjab Technical University,
S.B.S. Nagar-144533,
Railmajra, Punjab, India

ANSInet
Asian Network for Scientific Information

Department of Pharmaceutical Chemistry, Rayat Institute of Pharmacy, Punjab Technical University, S.B.S. Nagar-144533, Railmajra, Punjab, India

INTRODUCTION

Imides are the compounds in which nitrogen atom get linked to two carbonyl groups and consists of-CO-NH-CO structural grouping. These compounds are structurally related to derivatives of ammonia. These compounds can easily cross the biological membranes as they are neutral and hydrophobic in nature (Prado *et al*., 2004). The two hydrogen atoms of ammonia are replaced by carbonyl groups. Nitrogen atom in the imide moiety plays a significant role. Imide moiety plays an integral part in various important molecules such as thalidomide, isogranulatimide and rebeccamycin etc. These are the compounds which possess various pharmacological activities such as analgesic, anti-inflammatory, anti-depressant and anti-viral etc. (Abdel-Aziz, 2007). Imides and their derivatives are also used in polymer chemistry. Today various routes are available for the synthesis of imides which involve either Lewis-acid mediated condensation of an amine with maleic or phthalic anhydride or N-alkylation of the corresponding imide with halides or alcohols (Barchin *et al*., 2002). Various methods are used for the synthesis of imides and these methodologies and starting materials plays a significant role in their synthesis. The starting material, reaction conditions, reagents and selective methods leads to the better yield of these organic compounds which are more efficient. In synthetic organic chemistry, the development of selective methods with readily or easily available materials is the key task in their synthesis (Shinde *et al*., 2011). The discovery and development of Schiff bases of imide moiety are the most powerful and successful achievements of modern science and technology. A hetero cyclic compound plays an important role in regulating the biological activities. Schiff bases contain carbon-nitrogen double bonds in which nitrogen atom get linked to aryl and alkyl atoms. Schiff bases can possess different pharmacological activities and also have industrial applications. Schiff bases can be derived from aniline or o-amino phenol. These are the compounds containing characteristic -C = N- group. Schiff bases of imides possess different pharmacological activities such as antimicrobial, anti-inflammatory, antidepressant, antipyretic etc. (Vora *et al*., 2009; Da Silva *et al*., 2011). Schiff bases derived from ortho-hydroxyaryl aldehydes and aromatic or hetero aromatic amines have been synthesized in high yields via condensation in ethanol in the presence of catalytic amounts of sulfuric acid (Roman and Andrei, 2001; Ashraf *et al*., 2011). The development and synthesis of novel Schiff base derivatives as potential chemotherapeutics still attract the attention of organic and medicinal chemist. Besides their potential use as biologically active agents, Schiff bases and their metal complexes have been often used as chelating ligands in the coordination chemistry of transition metals and as radiopharmaceuticals for cancer targeting and agrochemicals (Hranjec *et al*., 2011). Compounds with the structure of AC = NB are known as Schiff bases, in which A and B are reacting material which are usually synthesized from the condensation of primary amines and active carbonyl groups (Shi *et al*., 2007). Schiff bases derived from aromatic ortho-hydroxy aldehydes have recently attracted considerable attention as new organic materials which could be utilised for designing various novel molecular devices (Koll *et al*., 2000). The synthesized Schiff bases can be used for their therapeutic potential. So the present study was carried out to synthesize Schiff bases of imides and to evaluate them for their analgesic and anti-inflammatory potential.

MATERIALS AND METHODS

Melting points were measured using Buchi melting point apparatus and are uncorrected. The ^{1}H-NMR spectra were recorded on a Bruker AC-300F, 300 MHz instrument using DMSO-d6 as solvent and Tetramethyl Silane (TMS) as internal reference standard. Thin-layer chromatography was performed on silica gel thin layer chromatographic plates using ethylacetate and hexane (3:7).

Drugs and chemicals: Carrageenan was obtained from Central Drug House Pvt. Ltd., Mumbai, India. 4-amino benzaldehyde was obtained from Oceanic laboratories Mumbai. Diclofenac sodium was obtained from Jackson Laboratories Pvt. Ltd., Amritsar. Silica gel G and acetone were obtained from E-Merk Pvt. Ltd., Mumbai. All other chemical reagents used were of analytical grade which were procured from different companies (Loba Chem, Mumbai and Merck Limited, Mumbai).

Animals: The Wistar albino rats (200-250 g) and Swiss albino mice (25-30 g) of either sex were obtained from Punjab Agricultural University Ludhiana. They were kept at standard laboratory diet, environmental temperature and humidity. The experimental protocol was duly approved by Institutional Animal Ethics Committee (IAEC) and care of the animals was carried out as per the guidelines of Committee for the Purpose of Control and Supervision of Experiments on Animals (CPCSEA).

Synthesis

4-(1,3-dioxoisoindolin-2-yl)benzaldehyde (1): A solution of 4-amino benzaldehyde (12.1 g, 0.1 mol) was prepared in

25 mL of dichloromethane and was added with stirring dropwise to a solution of phthalic anhydride (18.4 g, 0.1 mol) in 100 mL of dichloromethane. The reaction mixture was stirred for 8 h at 15-20°C. Then the mixture was treated with sodium bicarbonate (2 mg), water (5 mL) and solvent was removed under reduced pressure to obtain a residue. The product obtained was then poured in crushed ice and filtered. Then the product was crystallized in solvent ether to yield 1. The completion of reaction was monitored by TLC. Yield = 58%, m.p = 348.49°C, IR (KBr, cm^{-1}): 1756 (C = O), 1878 (-NH), 1510 (C = C), 1725 (-CHO) ^{1}H-NMR (DMSO-d6, δ, ppm): 7.3-7.6 (m, 2H, ArH), 7.8 (d, 2H, ArH), 7.93 (d, 2H, ArH), 8.17 (d, 2H, ArH), 9.97 (s, 1H, CHO).

Synthesis of Schiff bases

Schiff base 2-(4-(phenylimino) methyl) phenyl) isoindoline-1,3-dione (2) using aniline: A solution of compound 1 (0.1 mol) was prepared in ethanol 20 mL and was treated with aniline (10 mL) and 2-3 drops of conc. sulfuric acid in a 250 mL round bottom flask. The mixture was then refluxed for 8 h and then checked for completion by TLC. After cooling the obtained product was filtered then washed with water and dried. Recrystallization was done by using ethanol.

Yield = 52%, m.p = 396.55°C, IR (KBr cm^{-1}): 1715 (C = O), 2200 (-NH), 1527 (C = C), 2700 (HC = N). ^{1}H-NMR (DMSO-d6, δ, ppm): 7.1-7.46 (m, 5H, ArH), 7.66 (d, 2H, ArH), 7.86 (d, 2H, ArH), 7.96 (m, 2H, ArH), 8.13 (d, 2H, ArH), 8.39 (s, 1H, -CH = N-).

The steps involved in synthesis of Schiff bases of imide are presented in Fig. 1.

Schiff base 2-(4-[(4-nitrophenylimino) methyl) phenyl) isoindoline-1,3-dione (3) using p-nitro aniline: Equimolar quantities of compound 1 (0.1 mol) and p-nitro aniline (0.1 mol) were added into 20 mL of absolute ethanol containing a few drops of glacial acetic acid in a 250 mL round bottom flask. The reaction mixture was refluxed for half an hour and then checked for completion by TLC. The solvent was stripped off and the product was recrystallized from ethanol.

Yield = 48%, m.p. = 247.98°C, IR (KBr cm^{-1}): 1787 (C = O), 1827 (-NH), 1384 (C = NH), 1498 (NO_2), 1585

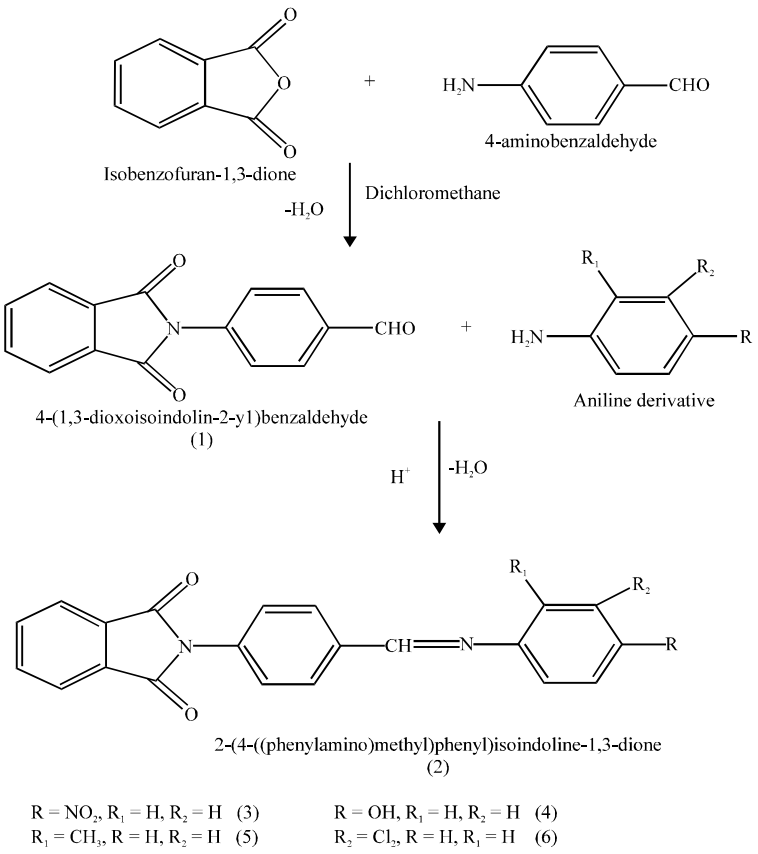


Fig. 1: Steps involved in the synthesis of Schiff bases of imide

(C = C). ^{1}H-NMR (DMSO-d6, δ, ppm): 7.5 (d, 2H, ArH), 7.63 (d, 2H, ArH), 7.65 (d, 2H, ArH), 7.73 (m, 2H, ArH), 7.84 (d, 2H, ArH), 8.19 (d, 2H, ArH), 8.39 (s, 1H, -CH = N-).

Schiff base (4) using p-hydroxy aniline: Equimolar quantities of compound 1 (0.1 mol) and p-hydroxy aniline (0.1 mol) were added into 20 mL of absolute ethanol containing a few drops of glacial acetic acid in a 250 mL round bottom flask. The reaction mixture was refluxed for half an hour and then checked for completion by TLC. The solvent was stripped off and the product was recrystallized from ethanol.

Yield = 59%, m.p. = 321.34°C, IR (KBr cm^{-1}): 3677 (OH), 1857 (C = O), 1582 (C = NH), 1624 (C = C), 2700 (C-H). ^{1}H-NMR (DMSO-d6, δ, ppm): 5.0 (s, 1H, OH), 6.7 (d, 2H, ArH), 7.1 (d, 2H, ArH), 7.60 (d, 2H, ArH), 7.67 (d, 2H, ArH), 7.69-7.79 (m, 2H, ArH), 8.13 (d, 2H, ArH), 8.39 (s, 1H, -CH = N-).

Schiff base 2-(4-((o-tolylimino) methyl) phenyl) isoindoline-1, 3-dione (5) using 2-methyl aniline: Equimolar quantities of compound 1 (0.1 mol) and 2-methyl aniline (0.1 mol) were added into 20 mL of absolute ethanol containing a few drops of glacial acetic acid in a 250 mL round bottom flask. The reaction mixture was refluxed for half an hour and then checked for completion by TLC. The solvent was stripped off and the product was recrystallized from ethanol.

Yield = 44%, m.p. = 376.44°C, IR (KBr cm^{-1}): 1475 (-CH3), 1856 (C = O), 1810 (-NH), 1525 (C = C). ^{1}H-NMR (DMSO-d6, δ, ppm): 2.5 (T, 3H, -CH3), 7.1-7.49 (m, 4H, ArH), 7.60 (d, 2H, ArH), 7.72 (d, 2H, ArH), 7.91 (m, 2H, ArH), 8.13 (d, 2H, ArH), 8.39 (s, 1H, -CH = N-).

Schiff base 2-(4-(3-chlorophenylimino)methyl)phenyl) isoindoline-1,3-dione(6) using 3-chloro aniline: Equimolar quantities of compound (1) (0.1 mol) and 3-chloro aniline (0.1 mol) were added into 20 mL of absolute ethanol containing a few drops of glacial acetic acid in a 250 mL round bottom flask. The reaction mixture was refluxed for half an hour and then checked for completion by TLC. The solvent was stripped off and the product was recrystallized from ethanol.

Yield = 53%, m.p. = 242.23°C, IR (KBr cm^{-1}): 785 (Cl), 1787 (C = O), 2067 (-NH). 1524 (C = C). ^{1}H-NMR (DMSO-d6, δ, ppm): 6.96 (s, 1H, ArH), 7.3-7.50 (m, 1H, ArH), 7.58 (d, 2H, ArH), 7.63 (d, 2H, ArH), 7.79 (d, 2H, ArH), 7.81-7.83 (m, 2H, ArH), 8.13 (d, 2H, ArH), 8.39 (s, 1H, -CH = N-).

Pharmacological evaluation: Ethanolic solution of synthesized compound was evaluated for its anti-inflammatory and analgesic activities using following model:

Anti-inflammatory activity

Carrageenan-induced rat paw edema: The carrageenan-induced rat paw edema assay was carried out according to Winter *et al.* (1962). Wistar rats were divided into 5 groups each consisting of 6 animals:

Group I : **Control:** Carboxymethyl cellulose (1% CMC, p.o.)+carrageenan
Group II : **Standard:** Diclofenac sodium (12.5 mg kg^{-1}, p.o.)+carrageenan
Group III: **Dose 1:** Ethanolic solution of synthesized compound (100 mg kg^{-1}, p.o.)+carrageenan
Group IV: **Dose 2:** Ethanolic solution of synthesized compound (200 mg kg^{-1}, p.o)+carrageenan
Group V : **Dose 3:** Ethanolic solution of synthesized compound (300 mg kg^{-1}, p.o.)+carrageenan

Edema was induced on the left hind paw of the rats by sub plantar injection of 0.1 mL of a solution of 1% (w/v) carrageenan in a 0.9% NaCl (w/v). The paw volume was measured at intervals of 60, 120, 180 min by the mercury displacement method using a plethysmograph after administration of the extract/drug orally. The percentage inhibition of paw edema in drug treated group was compared with the carrageenan control group and calculated according to the following formula:

$$\text{Inhibition (\%)} = \frac{V_t - V_c}{V_c} \times 100$$

where, V_c is the inflammatory increase in paw volume of control group of animals and V_t is the inflammatory increase in paw volume of drug-treated animals.

Analgesic activity: Swiss albino mice of either sex were divided into 5 groups each consisting of 6 animals:

Group I : **Control:** Carboxymethyl cellulose suspension (1% CMC, p.o.)
Group II : **Standard:** Diclofenac sodium at a dose of 10 mg kg^{-1} p.o.
Group III: **Dose 1:** Ethanolic solution of synthesized compound at a dose of 100 mg kg^{-1} p.o.
Group IV: **Dose 2:** Ethanolic solution of synthesized compound at a dose of 200 mg kg^{-1} p.o.
Group V : **Dose 3:** Ethanolic solution of synthesized compound at a dose of 300 mg kg^{-1} p.o.

Tail immersion test: The procedure is based on the observation that diclofenac sodium like drugs selectively prolongs the reaction time of the typical tail withdrawal reflex in mice (Toma *et al*., 2003). The tail of mice was immersed in warm water kept constant at 52.5±0.5°C. The reaction time of the tail-withdrawal response was determined at 60, 120 and 180 min after the administration of drugs. A cut off time of 15 sec was maintained to prevent tissue damage (Grotto and Sulman, 1967).

Hot plate method: The animals were divided into six groups of six animals each. Group I served as control and group II as standard and were injected diclofenac sodium (10 mg kg^{-1}) intraperitoneally. Group III, IV and V were treated orally with ethanolic solution of drug in doses of 100, 200 and 300 mg kg^{-1}. The animals were individually placed on the hot plate maintained at 55°C, one hour after their respective treatments. The animals were placed on the hot plate and the time until either licking or jumping occurs is recorded by a stop-watch. The latency is recorded before and after 60, 120 and 180 min following oral or subcutaneous administration of the standard or the test compound (Shukla *et al*., 2010).

Statistical analysis: All the results were expressed as Mean±Standard Error of Means (SEM). The data was statistically analyzed by one way Analysis of Variance (ANOVA) followed by Tukey's multiple range tests by using Sigmastat Version-2.0 Software. The $p<0.05$ was considered to be statistically significant.

RESULTS

In the present study, novel Schiff base derivatives of imides moiety have been synthesized by multistep reaction.

Synthesized compounds with their spectral data

4-(1,3-dioxoisoindolin-2-yl)benzaldehyde (1): ^{1}H-NMR spectrum exhibited multiplet at 7.3-7.6 (m, 2H, ArH), doublet at 7.8 (d, 2H, ArH), 7.93 (d, 2H, ArH), 8.17 (d, 2H, ArH) and singlet at 9.97 (s, 1H, CHO). IR spectrum bands at 1756, 1878, 1510 and 1725 confirms the presence of (C = O) (-NH) (C = C) and (-CHO), respectively.

2-(4-(phenylimino)methyl) phenyl) isoindoline-1,3-dione (2): ^{1}H-NMR spectrum exhibited multiplet at 7.1-7.46 (m, 5H, ArH), 7.96 (m, 2H, ArH) and doublet at 7.66 (d, 2H, ArH), 7.86 (d, 2H, ArH), 8.13 (d, 2H, ArH). IR spectrum bands at 1715, 2200, 1527, 2700 confirms the presence of (C = O), (-NH), (C = C) and (HC = N), respectively.

2-(4-[(4-nitrophenylimino)methyl)phenyl)isoindoline-1, 3-dione (3): ^{1}H-NMR spectrum exhibited doublet at 7.5 (d, 2H, ArH), 7.63 (d, 2H, ArH), 7.65 (d, 2H, ArH), multiplet at 7.73 and singlet at 8.39 (s, 1H, -CH = N-). IR spectrum showed bands at 1787, 1827, 1384, 1498, 1585 for (C = O) (-NH) (C = NH) (NO2) and (C = C).

2-(4-((4-hydroxyphenylimino)methyl)phenyl)isoindoline-1,3-dione (4): ^{1}H-NMR spectra showed multiplet at 7.69-7.79 (m, 2H, ArH), doublet at 6.7 (d, 2H, ArH), 7.1 (d, 2H, ArH), 7.60 (d, 2H, ArH), 7.67 (d, 2H, ArH) and singlet at 5.0 (s, 1H, OH), 8.39 (s, 1H, -CH = N-). IR spectrum showed bands at 3677, 1857, 1582, 1624, 2700 for (OH), (C = O), (C = NH), (C = C), (C-H), respectively.

2-(4-((o-tolylimino)methyl)phenyl)isoindoline-1,3-dione (5): ^{1}H-NMR spectra showed doublet at 7.60 (d, 2H, ArH), 7.72 (d, 2H, ArH), 8.13 (d, 2H, ArH), multiplet at 7.91 (m, 2H, ArH) and singlet at 8.39(s, 1H, -CH = N-). IR showed bands at 1475, 1856, 1810, 1525 (-CH3), (C = O), (-NH) and (C = C), respectively.

2-(4-(3-chlorophenylimino)methyl)phenyl)isoindoline-1,3-dione (6): ^{1}H-NMR spectra showed singlet at 6.96 (s, 1H, ArH), 8.39 (s, 1H, -CH = N-), doublet at 7.58 (d, 2H, ArH), 7.63 (d, 2H, ArH), 7.79 (d, 2H, ArH) and multiplet at 7.3-7.50 (m, 1H, ArH), 7.81-7.83 (m, 2H, ArH). IR spectrum showed bands at 785, 1787, 2067, 1524 for (Cl), (C = O), (-NH) and (C = C). The Schiff bases with imide moiety were evaluated for anti-inflammatory and analgesic property.

Physical properties: Various physical properties of the synthesized compounds were analyzed and are shown in Table 1.

Anti-inflammatory activity: Table 2 shows the results of the anti-edematous effect of orally administered ethanolic solution of synthesized compound on carrageenan induced paw edema in rats. The ethanolic solution of synthesized compound showed dose dependent anti-inflammatory activity in carrageenan induced paw edema in rats. At a maximum dose of 300 mg kg^{-1}, ethanolic solution of synthesized compound caused 58.8% reduction in paw edema. At other doses of 100 and 200 mg kg^{-1} the compound showed 14.70 and 44.11% inhibition of edema, respectively. All the values were significant ($p<0.05$) in comparison with control and standard.

Analgesic activity

Tail immersion test: Table 3 depicts the analgesic activity shown by ethanolic solution of synthesized

Table 1: Physical properties of prepared compounds

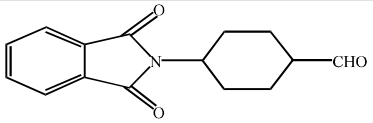
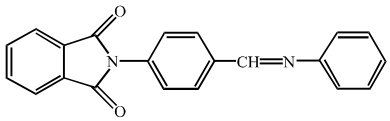
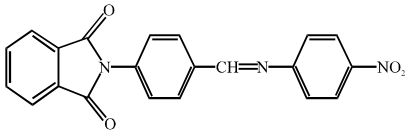
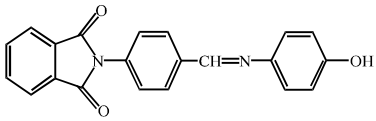
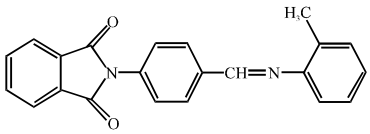
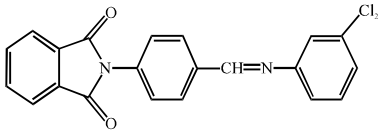
Comp. No.	Compound structure	Color	Melting points (°C)	Yield (%)	Solvent of recrystallization
1		Orange	348.49	58	Ether
2		Pale yellow	396.55	52	Ethanol
3		Deep yellow	247.98	48	Ethanol
4		Pale yellow	321.34	59	Acetone
5		Orange	376.44	44	Ethanol
6		Off white	242.23	53	Ethanol

Table 2: Effect of ethanolic solution of Schiff bases of imides on carrageenan-induced paw edema in rats

		Paw volume (mL)			
Group	Dose (mg kg^{-1}) orally	60 min	120 min	180 min	Inhibition of edema (%)
Control	1% CMC	0.47±0.003	0.55±0.008	0.68±0.003	-
Diclofenac sodium	10	0.41±0.006[a]	0.35±0.005[a]	0.23±0.003[a]	66.17
Dose 1	100	0.45±0.005	0.51±0.005	0.58±0.002	14.70
Dose 2	200	0.44±0.003[ab]	0.41±0.007[ab]	0.38±0.001[ab]	44.11
Dose 3	300	0.38±0.002[ab]	0.39±0.420[ab]	0.28±0.004[ab]	58.82

Values are Mean±SEM of 6 animals in each group, [a]p<0.05 compared with disease control group, [b]p<0.05 compared with diclofenac sodium treated group

Table 3: Analgesic effect of Schiff bases of imides by tail immersion test

		Tail withdrawal latency (sec)		
Group	Dose (mg kg^{-1}) orally	60 min	120 min	180 min
Control	1% CMC	2.50±0.01	2.74±0.01	2.90±0.01
Diclofenac sodium	10	9.90±0.01[a]	10.44±0.02[a]	14.23±0.06[a]
Dose 1	100	3.71±0.05	4.88±0.01	5.73±0.04
Dose 2	200	5.60±0.08[ab]	6.58±0.023[ab]	8.38±0.18[ab]
Dose 3	300	7.25±0.14[ab]	8.82±0.029[ab]	10.47±0.04[ab]

Values are Mean±SEM of 6 animals in each group, [a]p<0.05 compared with disease control group, [b]p<0.05 compared with diclofenac sodium treated group

compound by tail immersion method. Ethanolic solution of synthesized compound showed dose dependent analgesic activity against conduction of heat-induced algesia in mice. After 3 h a maximum dose of 300 mg kg^{-1} showed significant difference in the analgesic activity when compared with control group in which the reaction time of 10.47±0.04 sec was observed. At lower doses of 100 and 200 mg kg^{-1} the extract showed the reaction time of 5.73±0.04 and 8.38±0.18 sec, respectively after 3 h. All the values were significant ($p<0.05$) in comparison with control and standard.

Hot plate method: Table 4 shows the results of analgesic activity shown by ethanolic solution of synthesized compound by hot plate method. The given compound showed maximum analgesic activity after 3 hours at a maximum dose of 300 mg kg^{-1} with the reaction time of 12.24±0.01 seconds. At lower doses of 100 mg kg^{-1} and 200 mg kg^{-1} the reaction time of 7.13±0.01 and 10.33±0.05 sec, respectively was noted after 3 h. All the values were significant ($p<0.05$) in comparison with control and standard.

Table 4: Analgesic effect of Schiff bases of imides by hot plate method

Group	Dose (mg kg^{-1}) orally	Reaction time (sec) 60 min	120 min	180 min
Control	1% CMC	3.82±0.01	4.07±0.008	4.13±0.01
Diclofenac sodium	10	8.32±0.04[a]	12.13±0.070[a]	13.84±0.06[a]
Dose 1	100	7.07±0.03	7.07±0.003	7.13±0.01
Dose 2	200	7.81±0.10[ab]	9.48±0.020[ab]	10.33±0.05[ab]
Dose 3	300	10.38±0.01[ab]	11.41±0.010[ab]	12.24±0.01[ab]

Values are Mean±SEM of 6 animals in each group, [a]$p<0.05$ compared with disease control group, [b]$p<0.05$ compared with diclofenac sodium treated group

DISCUSSION

According to the synthetic methodology of imides, various methods, reagents and reaction conditions have been already described for the synthesis of imides which exhibit various pharmacological activities. For example: the b-alkylidene succinanilic acids on treatment with cyanuric chloride in the presence of triethylamine yields b-alkylisomaleimides. The Wittig condensation of alkyl substituted isomaleimides/maleimides with aliphatic aldehydes gave the desired dialkyl substituted maleimides had already been described (Haval and Argade, 2006). Formamide was used as reagent for the synthesis of various aliphatic and aromatic imides with cyclic carboxylic anhydrides. The reaction was carried out at 170-180°C for 5-6 h (Chiriac *et al*., 2007). In the present study, the imide 4-(1,3-dioxoisoindolin-2-yl)benzaldehyde has been synthesized by reacting phthalic anhydride and 4-amino benzaldehyde in the presence of dichloromethane. Dichloromethane was used as a reagent to form product with better yield. From the above mentioned imide moiety, different derivatives of Schiff bases of imides have been synthesized. Various other methods of synthesis of imide derivatives are discovered which are carried out in different conditions in which primary and secondary alcohols are converted to esters (Benjamin and Hijji, 2008). Various pharmacological activities have been noticed from imide derivatives. Schiff bases of 4-amino benzaldehyde showed anti-bacterial activity (Parekh *et al*., 2005). Some novel cyclic-imides were found to possess hypoglycaemic, anti-hyperlipidemic activity. Various pharmacological activities have been shown by halogenated cyclic imides which are derived from N-substituted phthalimide moiety (Abdel-Aziz *et al*., 2011). The cyclic anhydrides and imides are the compounds of choice for all chemists from both the basic and applied point of view for multiple purposes (Haval and Argade, 2006). Since imides are a valuable group of bioactive compounds showing various pharmacological activities. Therefore, the target of present research work has been directed towards the synthesis of novel Schiff bases of imide moiety with expected biological activities (Orzeszko *et al*., 2001). For the discovery of new analgesic drugs, cyclic imides like 1,8-naphthalimide and 1,4,5,8-naphthalene diimide were prepared and their analgesic properties were evaluated by using the writhing test in mice (Andricopulo *et al*., 2000). According to literature review, imides have been evaluated for various pharmacological activities, so in this research Schiff bases of imides have been evaluated for their anti-inflammatory and analgesic potential (Rana *et al*., 2012; Okunrobo *et al*., 2006; Gaikwad *et al*., 2010). Tail immersion and hot plate methods were carried out to evaluate the analgesic potential of Schiff bases of imides. Results of the study indicate the significant decrease in the reaction time of tail withdrawal by ethanolic solution of Schiff bases of imides. It shows that ethanolic solution of Schiff bases of imides possesses analgesic property. This analgesic activity may be due to its free radical scavenging activity as these free radicals are involved during pain stimulation and antioxidants show reduction in such pain (Kim *et al*., 2004). The synthesized compound was further evaluated for its *in vivo* anti-inflammatory potential. Carrageenan induced rat paw edema test has frequently been used to assess the anti-edematous effect of the synthesized compound. Carrageenan is used to cause inflammation and it helps in releasing various inflammatory mediators like prostaglandins, leukotrienes, histamine, bradykinin etc. (Crunkhorn and Meacock, 1971). Decrease of edema in rat paw indicated that the ethanolic solution of Schiff bases of imides possess anti-inflammatory activity. Thus, the synthesized Schiff bases of imides can be employed as analgesic and anti-inflammatory agent.

CONCLUSION

The present study demonstrated that synthesized Schiff bases of imides possess various significant pharmacological activities like analgesic and anti-inflammatory properties at high dose level which was comparable to that of standard drug. Therefore, these compounds can be used in the treatment of various pains and inflammation.

ACKNOWLEDGMENTS

Thanks to Professor A.C. Rana and all faculty members of Rayat Institute of Pharmacy for their encouragement and support. We are also grateful to Rayat and Bahra Educational and Research Trust for their unconditional help to carry out this project.

REFERENCES

Abdel-Aziz, A.A., A.S. El-Azab, S.M. Attia, A.M. Al-Obaid, M.A. Al-Omar and H.I. El-Subbagh, 2011. Synthesis and biological evaluation of some novel cyclic-imides as hypoglycaemic, anti-hyperlipidemic agents. Eur. J. Med. Chem., 46: 4324-4329.

Abdel-Aziz, A.A.M., 2007. Novel and versatile methodology for synthesis of cyclic imides and evaluation of their cytotoxic, DNA binding, apoptotic inducing activities and molecular modeling study. Eur. J. Med. Chem., 42: 614-626.

Andricopulo, A.D., L.A. Muller, V.C. Filho, G.S. Cani and J.F. Roos *et al*., 2000. Analgesic activity of cyclic imides: 1,8-naphthalimide and 1,4,5,8-naphthalenediimide derivatives. Il Farmaco, 55: 319-321.

Ashraf, M.A., K. Mahmood and A. Wajid, 2011. Synthesis, characterization and biological activity of Schiff bases. IPCBEE, 10: 1-7.

Barchin, B.M., A.M. Cuadro and J. Alvarez-Builla, 2002. Microwave-assisted parallel synthesis of a 2-Aryl-lH-Isoindole-l, 3-dione. Synlett, 2: 343-345.

Benjamin, E. and Y. Hijji, 2008. The synthesis of unsubstituted cyclic imides using hydroxylamine under microwave irradiation. Molecules, 13: 157-169.

Chiriac, C.I., M. Nechifor and F. Tanasa, 2007. Formamide, a novel challenging reagent for the direct synthesis of non-n-substituted cyclic imides. Revue Roumaine Chimie, 52: 883-886.

Crunkhorn, P. and S.C.R. Meacock, 1971. Mediators of the inflammation induced in the rat paw by carrageenin. Br. J. Pharmacol., 42: 392-402.

Da Silva, C.M., D.L. da Silva, L.V. Modolo, R.B. Alves, M.A. de Resende, C.V.B. Martins and A. de Fatima, 2011. Schiff bases: A short review of their antimicrobial activities. J. Adv. Res., 2: 1-8.

Gaikwad, K.V., S.V. Gaikwad, S.B. Jadhav and S.D. Rathod, 2010. Synthesis of some novel chalcones of phthalimidoester possessing good anti-inflammatory and antimicrobial activity. Ind. J. Chem., 49: 131-136.

Grotto, M. and F.G. Sulman, 1967. Modified receptacle method for animal analgesimetry. Arch. Int. Pharmacodyn. Ther., 165: 152-159.

Haval, K.P. and N.P. Argade, 2006. Haval-argade contrathermodynamic rearrangement of alkylidenesuccinimides to alkylmaleimides via the corresponding isoimides: A general approach to alkyl and dialkyl substituted maleimides. Tetrahedron, 62: 3557-3563.

Hranjec, M., K. Starcevic, S.K. Pavelic, P. Lucin, K. Pavelic and G.K. Zamola, 2011. Synthesis, spectroscopic characterization and antiproliferative evaluation *in vitro* of novel Schiff bases related to benzimidazoles. Eur. J. Med. Chem., 46: 2274-2279.

Kim, H.K., S.K. Park, J.L. Zhou, G. Taglialatela, K. Chung, R.E. Coggeshall and J.M. Chung, 2004. Reactive oxygen species (ROS) play an important role in a rat model of neuropathic pain. Pain, 111: 116-124.

Koll, A., M. Rospenk, E. Jagodzinska and T. Dziembowska, 2000. Dipole moments and conformation of Schiff bases with intramolecular hydrogen bonds. J. Mol. Struct., 552: 193-204.

Okunrobo, L.O., C.O. Usifoh and S.O. Okpo, 2006. Reactions of phthalimides with 1-methylethylamine: Aanalgesic and anti-inflammatory properties of resulting carboxamides. Pak. J. Pharm. Sci., 19: 34-38.

Orzeszko, A., B. Kaminska and B.J. Starosciak, 2001. Synthesis and antimicrobial activity of new adamantane derivatives III. Farmaco, 57: 619-624.

Parekh, J., P. Inamdar, R. Nair, S. Baluja and S. Chanda, 2005. Synthesis and antibacterial activity of some Schiff bases derived from 4-amino benzoic acid. J. Serb. Chem. Soc., 70: 1115-1161.

Prado, S.R., V. Cechinel-Filho, F. Campos-Buzzi, R. Correa, S.M. Cadena and M.B. de Oliveira, 2004. Biological evaluation of some selected cyclic imides: Mitochondrial effects and *in vitro* cytotoxicity. Z. Naturforsch C, 59: 663-672.

Rana, K., A. Pandurangan, N. Singh and A.K. Tiwari, 2012. A systemic review of Schiff bases as an analgesic, anti-inflammatory. Int. J. Curr. Pharma. Res., 4: 5-11.

Roman, G. and M. Andrei, 2001. New Schiff bases from *ortho*-hydroxyaryl aldehydes. Bull. Chem. Tech. Mac., 20: 131-136.

Shi, L., H.M. Ge, S.H. Tan, H.Q. Li, Y.C. Song, H.L. Zhu and R.X. Tan, 2007. Synthesis and antimicrobial activities of Schiff bases derived from 5-chloro-salicylaldehyde. Eur. J. Med. Chem., 42: 558-564.

Shinde, S.B., S.U. Tekale, S.S. Kauthale, S.U. Deshmukhb and R.P. Marathe *et al*., 2011. A facile and efficient synthesis of N-aryl imides using trifluoroacetic acid. Int. J. Ind. Chem., 2: 112-116.

Shukla, S.H., H.A. Mistry, V.G. Patel and B.V. Jogi, 2010. Pharmacognostical, preliminary phytochemical studies and analgesic activity of *Amomum subulatum*. Pharm. Sci. Monitor, 1: 90-102.

Toma, W., J.S. Graciosa, C.A. Hiruma-Lima, F.D.P. Andrade, W. Vilegas and A.R.M. Souza-Brita, 2003. Evaluation of the analgesic and antiedematogenic activities of *Quassia amara* bark extract. J. Ethnopharmacol., 85: 19-23.

Vora, J.J., S.B. Vasava, K.C. Parmar, S.K. Chauhan and S.S. Sharma, 2009. Synthesis, spectral and microbial studies of some novel Schiff base derivatives of 4-Methylpyridin-2-amine. Eur. J. Chem., 6: 1205-1210.

Winter, C.A., E.A. Risley and G.W. Nuss, 1962. Carrageenan-induced edema in hind paw of the rat as an assay for anti-inflammatory drugs. Proc. Soc. Exp. Biol. Med., 111: 544-547.