Synthesis and characterization of 2-(substituted)-1-(substituted)-4,5-diphenyl-1*H*-imidazole as potent analgesic agents

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ABSTRACT

A novel series of substitute imidazole derivatives were synthesized and their analgesic activity was evaluate using Eddy's hot plate method. In the first step, substituted amines were allowed to react with substituted benzaldehyde in an equimolar amount with glacial acetic acid to form various substituted Schiff's base intermediate **(1a-h).** Schiff's base on treatment with benzil in the presence of ammonium acetate afforded corresponding imidazole derivatives (**2a-h**). The structure of the final analogs has been confirmed on the basis of elemental analysis, fourier transform infrared spectroscopy (FT-IR), ^{1}H nuclear magnetic resonance (NMR), 13C NMR, and mass spectra. The compound **2b** and **2c** was found to be most effective compound compared to the Diclofenac conventional drug. Eddy's hot plate method was utilized to evaluate the test compounds for their *in vivo* analgesic activity.

KEYWORDS: Imidazole, analgesic activity, Sciff base, Eddy hot plate.

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INTRODUCTION

Pain is an unpleasant sensation that causes discomfort and reduces both physical and mental alertness. Analgesics, which are widely used medications for the treatment of pain, can be divided into two groups: morphine-related drugs and NAIDS (non-steroidal anti-inflammatory drugs). Pain is also beneficial for us because it serves as a warning signal and alerts us to something unusual inside or outside of our bodies. NSAIDS primarily work by preventing the COX (cyclooxygenase) enzymes, which catalyse the first stage in prostaglandin production, from acting. NSAIDs may have serious G.I. (Gastrointestinal) adverse effects when used for an extended period of time, which restricts the use of these medications [1-3].

The adverse effects associated to the use of non-selective NSAIDs result from a decrease in the amount of protective prostaglandin in the GI (gastrointestinal tract) due to COX-1 inhibition. Although selective COX 2 inhibitors have a less damaging effect on the GI tract than non-selective NSAIDs, their use in treatment is still limited because of their negative cardiovascular effects [9-11]. It is clear from the discussion above that the search for a novel active compound has grown significantly in importance. Imidazole derivatives have been found occupy analgesic activity [4-6].

Medicinal chemists have carried out considerable research for innovative analgesic agents which possess carboxylic acid moiety. The prominent compounds bearing the R-COOH (carboxylic acid) group are aspirin, ibuprofen, and naproxen, all of which are extensively used as over-the counter drugs for the alleviation of pain. Several studies have been confirmed that imidazole derivatives possess analgesic activity. The synthesis of various derivatives of imidazole has got massive attention in recent years as this class of compounds constitutes structural frameworks of several naturally occurring compounds displaying a wide range of biological activities such as anti-microbial, anti-cancer, anti-tubercular, anti-HIV, anti-oxidant, anti-fungal, anti-bacterial, anti-convulsant, anti-hypertensive, and anti-diabetic activity. Since imidazole moiety exerts analgesic and anti-inflammatory activities [7-18].

MATERIAL AND METHOD

Chemistry:

All research chemicals used were from purchased from Spectrochem Pvt. Ltd., Mumbai, Central Drug House Pvt.Ltd., New Delhi, and Loba Chemie Pvt.Ltd. Mumbai. The melting points were resolved in an open capillary tube using electro thermal digital melting apparatus. (Science Tech. Pvt, Ltd. Maharashtra India). TLC checked the purity of all the synthesized compounds on silica gel 60 F254 and spots were determined by UV-lamp at λ 254 nm. Spectroscopic data were recorded on PerkinElmer FT-IR Spectrometer using KBr pressed pellet technique, and vmax is expressed in cm^{-1}.NMR spectra were measured in DMSO-d6 as a solvent at Bruker DRX-300 (1H NMR) spectrometer using tetra methylsilane (TMS) as the internal standard. δ (Chemical shift) was indicated in ppm (parts per million). All the solvent were distilled and dried with usual moisture less.

Synthesis:

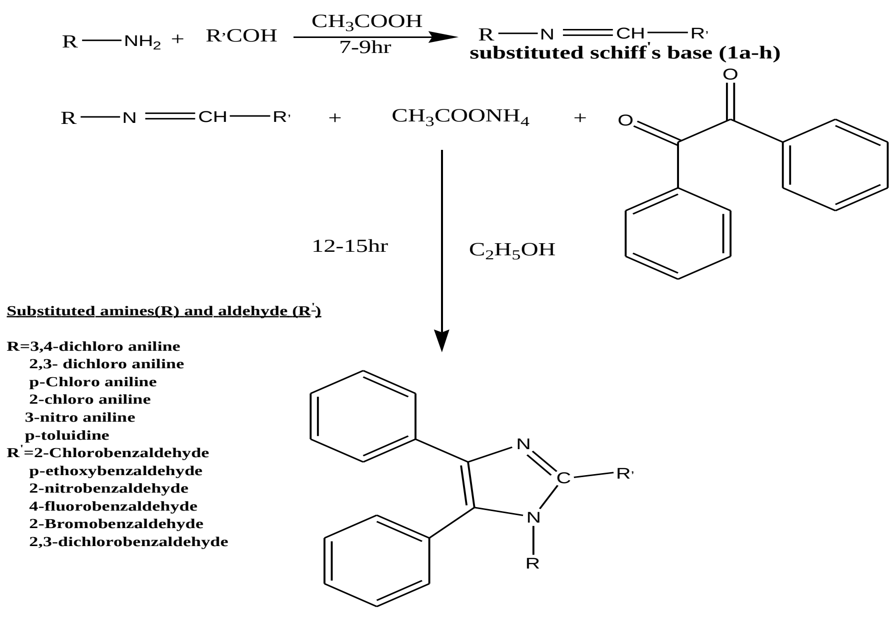
General procedure for synthesis of substituted Schiff bases (1a-h)

Equimolar amount (0.01 M) of substituted benzaldehyde and substituted aromatic amine were added to glacial acetic acid (20 ml) in a small evaporating dish. Reaction mixture placed on a boiling water bath with stirring for 7-9 h. On completion of reaction, the reaction mixture was placed in cold water with stirring. After solidification reaction mixture was recrystallized using rectified spirit to give substituted Schiff's base [19-20].

General procedure for synthesis of aryl imidazole derivatives (2a-h)

Schiff 's base (0.01 M) was transferred in the presence of excess ammonium acetate (0.1 M) in to a flask containing benzil (0.01 M). The reaction mixture was refluxed for about 12-15 h. The progress of the completion of reaction was monitored by TLC. Then, the reaction mixture was poured in to 250 ml of water to remove ammonium acetate and acetic acid. The precipitate was filtered, washed with benzene (2× 30 m) to remove traces of any unreacted benzil and recrystallized from ethyl acetate to give corresponding imidazole derivatives.

Scheme:



(2a-h)

2-(2,6-dichlorophenyl)-1-(4-ethoxyphenyl)-4,5-diphenyl-1H-imidazole (2a)

Yield 60 %; R_f =0.71; white crystal; mp 198-199°C; FT-IR (KBr, ν, cm^{-1}): 3020.55 (Ar, C-H str), 3511.44 (Ali, C-H str), 1583.09 (Ar, C=C str), 1645.38 (C=N), 1321.25 (C-N), 1207.23 (C-O-C Asymmetric) 1038.23 (Ar. C-Cl); ^{1}H NMR (300 MHz, DMSO-d6): 1.81 (s, 3H, $-CH_3$) 3.11 (s, 2H, -OCH_2), 6.36-6.89 (m, 6H, Ar H), 7.09-7.27 (m, 5H, Ar H), 7.32-7.61 (m, 6H, Ar-H). Anal. Calcd. for $C_{29}H_{22}Cl_2N_2O$: C, 73.39; H, 5.27; N, 5.18, Found: C, 73.37; H, 5.27; N, 5.15%.

2-(2,3-dichlorophenyl)-1-(2-chlorophenyl)-4,5-diphenyl-1H-imidazole (2b)

Yield 58 %; R_f =0.61; white crystal; mp 280-282°C; FT-IR (KBr, ν, cm−1): 3040.8 (Ar, C-H str), 3323.88 (Ali, C-H str), 1584.54 (Ar, C=C str), 1641.34 (C=N), 1339.20 (C-N), 765.75 (C-O-C Asymmetric) 1030.65 (Ar. C-Cl); ^{1}H NMR (300 MHz, DMSO-d6): 1.81 (s, 3H, $-CH_3$) 3.11 (s, 2H, -OCH_2), 6.44-6.76 (m, 5H, Ar H), 6.82-7.03 (m, 3H, Ar H), 7.11-7.30 (m, 4H, Ar-*H).* Anal. Calcd. for $C_{27}H_{17}Cl_3N_2$ *: C*, 68.16; H, 3.60, N, 5.89, Found: C, 68.14; H, 3.58; N, 5.87%.

2-(4-chlorophenyl)-1-(2-nitrophenyl)-4,5-diphenyl-1H-imidazole (2c)

Yield 63 %; R_f =0.65; white crystal; mp 241-242°C; FT-IR (KBr, ν, cm−1): 3023.93 (Ar, C-H str), 3311.78 (Ali, C-H str), 1579.47 (Ar, C=C str), 1649.67 (C=N), 1334.20(C-N), 773.94 (Ar. C-Cl); ^{1}H NMR (300 MHz, DMSO-d6): , 6.03-6.33 (m, 6H, Ar H), 6.48-7.12 (d, 5H, Ar H), 7.29.7.77 (m, 7H, Ar-H*).* Anal. Calcd. for $C_{27}H_{18}ClN_3O_2$*:* C, 71.76; H, 4.01; N, 9.30, Found: C, 71.75; H, 3.99; N, 9.28%.

2-(2,3-dichlorophenyl)-1-(4-fluorophenyl)-4,5-diphenyl-1H-imidazole (2d)

Yield 45 %; Rf =0.73; white crystal; mp 165-166°C; FT-IR (KBr, ν, cm−1): 3078.42 (Ar, C-H str), 3559.71 (Ali, C-H str), 1599.07 (Ar, C=C str), 1653.39 (C=N), 1363.39 (C-N), 1030.65 (Ar. C-Cl); ^{1}H NMR (300 MHz, DMSO-d6): 6.44-6.76 (m, 7H, Ar H), 7.11-7.34 (m, 3H, Ar H), 7.46-7.66 (m, 7H, Ar-H). Anal. Calcd. for $C_{27}H_{17}Cl_2FN_2$ *: C*, 70.60; H, 3.73; N, 6.10, Found: C, 73.87; H, 4.47; N, 6.17%.

2-(2,3-dichlorophenyl)-1-(3-methoxyphenyl)-4,5-diphenyl-1H-imidazole (2e)

Yield 55 %; R_f =0.57; white crystal; mp 236-237°C; FT-IR (KBr, ν, cm^{-1}): 3042.25 (Ar, C-H str), 3439.68 (Ali, C-H str), 1586.46 (Ar, C=C str), 1386.87(C=N), 1323.76 (C-N), 1205.29(C-O-C Asymmetric) 1039.20 (Ar. C-Cl); ^{1}H NMR (300 MHz, DMSO-d6): 3.54 (s, 3H, $-OCH_3$), 6.48-6.88(m, 7H, Ar H), 7.01.-7.21(d, 3H, Ar H), 7.34-7.41 (m, 7H, Ar-H). *).* Anal. Calcd. for $C_{28}H_{20}Cl_2N_2O$*:* C, 71.34; H, 4.28; N, 5.94, Found: C, 71.32; H, 4.26; N, 5.92%.

1-(2-bromophenyl)-2-(2-chlorophenyl)-4,5-diphenyl-1H-imidazole (2f)

Yield 72 %; R_f =0.67; white crystal; mp 218-219°C; FT-IR (KBr, ν, cm^{-1}): 3046.56 (Ar, C-H str), 3519.61(Ali, C-H str), 1580.29 (Ar, C=C str), 1637.37 (C=N), 1329.84 (C-N), 1038.23 (Ar. C-Cl); 543.89(C-Br) ^{1}H NMR (300 MHz, DMSO-d6): 6.51-7.02 (m, 7H, Ar H), 7.34-7.51 (d, 4H, Ar H), 7.64-7.95 (m, 7H, Ar-H). *).* Anal. Calcd. for $C_{27}H_{18}BrClN_2$*:* C, 66.75; H, 3.73; N, 5.77, Found: C, 66.73; H, 3.71; N, 5.75%.

1-(2,3-dichlorophenyl)-2-(3-nitrophenyl)-4,5-diphenyl-1H-imidazole(2g)

Yield 64 %; R_f =0.77; white crystal; mp 210-211°C; FT-IR (KBr, ν, cm^{-1}): 3056.78 (Ar, C-H str), 3540.87 (Ali, C-H str), 1532.64 (Ar, C=C str), 1670.71 (C=N), 1395.80 (C-N), 1073.75 (Ar. C-Cl); ^{1}H NMR (300 MHz, DMSO-d6): , 7.03-7.27 (m, 7H, Ar H), 7.34.7.51 (d, 3H, Ar H), 7.64-7.95 (m, 7H, Ar-H). *).* Anal. Calcd. for $C_{27}H_{17}Cl_2N_3O_2$*:* C, 66.68; H, 3.52; N, 8.64, Found: C, 66.66; H, 3.50; N, 8.62%.

1-(4-methoxyphenyl)-4,5-diphenyl-2-p-tolyl-1H-imidazole (2h)

Yield 75 %; R_f =0.79; white crystal; mp 287-288°C; FT-IR (KBr, ν, cm^{-1}): 3088.90(Ar, C-H str), 3565.81 (Ali, C-H str), 1523.42 (Ar, C=C str), 1621.74(C=N), 1328.96 (C-N), 1209.90 (C-O-C Asymmetric) 1038.23 (Ar. C-Cl); ^{1}H NMR (300 MHz, DMSO-d6): 1.97 (s, 3H, $-CH_3$) 3.23 (s, 3H, -OCH_3), 6.38.-7.01 (m, 4H, Ar H), 7.11-7.21 (d, 7H, Ar H), 7.36.-7.77 (m, 7H, Ar-H).). Anal. Calcd. for $C_{27}H_{24}N_2O$ *:* C, 83.67; H, 5.81; N, 6.73, Found: C, 83.65; H, 5.79; N, 6.71%.

Table 1: Physicochemical parameters of synthesized compounds (2a-h)

Compound code	Molecular formula	Molecular weight	% yield	R_f value	M.P. (ºC)
2a	$C_{29}H_{22}Cl_2N_2O$	485.4	62.07	0.71	198-199
2b	$C_{27}H_{17}Cl_3N_2$	475.8	59.46	0.61	280-281
2c	$C_{27}H_{18}ClN_3O_2$	451.9	70.29	065	241-242
2d	$C_{27}H_{17}Cl_2FN_2$	459.34	59.06	0.73	165-166
2e	$C_{28}H_2OCl_2N_2O$	471.38	69.36	0.57	236-237
2f	$C_{27}H_{18}BrClN2$	485.8	78.45	0.67	218-219
2g	$C_{27}H_{17}Cl_2N_3O_2$	486.35	67.54	0.77	210-211
2h	$C_{27}H_{24}N_2O$	416.51	72.56	0.79	287-288

Pharmacological Screening:

Animals: Swiss albino mice of the male sexual categories weighing 25-30g were obtained. The animal were separated in to several groups. All the animals were housed under standard ambient environment of temperature (25±2ºC) and relative humidity of 35-60%. 12h light and dark cycles were maintained. All the animals were allowed to have the generosity to water and standard palletized laboratory animal diet 12 h previous to pharmacological studies. All the investigational procedures and protocols used in this study were reviewed and recognized by the IAEC (Institutional Animal Ethical Committee), Hygia Institute of pharmaceutical Education and Research, Lucknow, India Approval No. (HIPER/IAEC/ 90/02/2022).

Eddy's Hot Plate Method:

The compounds exhibit an important analgesic activity measured by Eddy's hot plate method. Animal were divided in to different groups. Animals were kept deprived of food 12 h before drug administration till the activity gets completed. Animals were weighed and numbered appropriately. Animal were individually placed on a hot plate maintained at a temperature (55±1ºC) and the reaction of animals, such as paw licking or jump response (whichever appears first) was taken as the end point. A cut-off time of 15 seconds was taken as a maximum analgesic response to escape injury to the paws. The Standard group received diclofenac sodium (10/mg/kg) oral route. Synthesized compounds were administered orally to the test groups (30/mg/kg). Analgesic activity of synthesized compounds was estimated at equimolar doses. The basal reaction time was recorded at 30/60/90 and 120 min administration of the standard or the test compound [21-22].

RESULTS AND DISCUSSION

Chemistry: As per scheme imidazole derivatives were prepared in two steps. The first step substituted benzaldehyde and substituted amine react with in the presence of glacial acetic acid afford the corresponding sciff's bases. sciff's bases were allowed to react with ammonium acetate and benzyl to give corresponding imidazole derivatives.

Infrared (IR) spectra of all final imidazole derivatives showed a strong, characteristic band in the region 1215-1389 cm^{-1} due to the C-N stretching vibration. The IR spectra of products showd an intense peak in the region 1566-1592 cm^{-1} due to the C=N stretching vibration which confirms indicating the presence of C=N at imidazole ring the conversion of substrates into the expected products [23-30].

Biological Evaluation:

Analgesic activity:

Eddy's hot plate method was utilized to evaluate the test compounds for their *in vivo* analgesic activity. Analgesic obtained for the test compounds were compared with the control group. Data are expressed as Mean reaction time ± S.E.M. analyzed by two-way ANOVA, followed by Dunnett's test. Diclofenac at a dose 10 mg/kg exhibited significant analgesic activity ($p<0.01$) at all-time intervals as compared to the control group. As shown in table 3 all the compounds **2b-2c** exhibited varying degrees of analgesic activity. Compounds **2b** and **2c** were found to exhibit potent analgesic activity.

Table 2: Analgesic activity data of compounds using Eddy's hot plate method

Compound	Before treatment BMT (sec) (Mean±SEM)	After treatment BMT (sec) (Mean±SEM)			
		15 min	½ hr	1 hr	2 hr
2a	3.85	5.10	5.29	5.70	5.52
2b	**4.16*****	**8.49****	**8.74****	**9.09****	**10.19****
2c	**3.74****	**6.30****	**6.95***	**7.49****	**8.12***
2d	3.83	4.10	4.43	4.65	4.90
2e	4.09	6.10	6.30	6.86	7.10
2f	3.98	5.34	5.63	5.96	6.23
2g	3.89	5.28	5.57	5.89	6.16
2h	3.74	5.17	5.48	5.74	6.07
Control	4.31	4.23	4.27	4.11	4.17
Standard	4.26	10.32	11.87	12.35	13.65

Data are expressed as Mean ±SEM for Statistical Analysis was Performed

CONCLUSION

An innovative series of different imidazole derivatives were synthesized and screened for analgesic activity by using Eddy's hot plate method respectively. Physical and analytical parameters of the newly synthesized imidazole derivatives were confirmed by melting point, TLC, IR, ^{1}HNMR and mass spectra. Subsequently, in biological screening, the compound **2b** and **2c** showed potent analgesic as compared to the other derivatives. Further research on imidazole is needed for discovery as a potent analgesic agent.

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