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Research Article

SYNTHESIS AND PHARMACOLOGICAL EVALUATION OF 1,5 – DIARYLIMIDAZOLES

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ABSTRACT

The synthesis and pharmacological activity of a new series of 1,5 - diarylimidazoles as potent selective COX – 2 inhibitor are described. The new compounds were evaluated in vivo (carrageenan induce paw oedema). Structural modification was done at all position in 1,5 – diarylimidazole cores for identification of lead compound.

Keywords: 1,5 - diarylimidazoles, selective COX – 2 inhibitor, carrageenan induce paw oedema.

INTRODUCTION

Inhibition of Cycloxygenese (COX), one of the key enzymes in arachidonic acid (AA) cascade is the main mechanism which non-steroidal anti-inflammatory drugs (NSAIDs) exerts their anti-inflammatory activity. This enzyme bis-oxygenate AA to PGG_2, which is sub-sequently degraded to vasoactive and inflammatory mediators such as Prostaglandins (PGs), Prostacyclin (PGI_2) and Thromboxan – A_2. The therapeutic use of NSAIDs, especially in chronic diseases, has revealed their association with well-known side effects at the gastrointestinal level (mucosal damage, bleeding) and less frequently, at the renal level.[1]

After the discovery a decade ago of two COX iso forms, it was recognized that selective inhibitors of the inducible form (COX – 2, Cytokine inducible, and expressed mainly in inflammatory cells) could provide anti-inflammatory agents devoid of the undesirable effects associated with classical non selective NSAIDs. The inhibition of COX – 1, the form constitutively present in many tissues such as stomach, kidney and platelets, by non-selective NSAIDs may be responsible for the secondary effects associated with their use.

Although modification of established non-selective agents, such as lengthening the carboxyl side chain of indomethacine, have been strategies for the design of COX – 2 selective inhibitors, the main effort has been addressed to the diarylheterocycles class, based an early known anti-inflammatory drugs, such as Flumizole.[1]

As new approach to diarylheterocycle class COX – 2 inhibitors we report here the pharmacological studies of new 1,5 – diarylimidazoles in which defined combination of substituents confers appropriate polarity and charge distribution for good activity.

EXPERIMENTAL

Melting point were uncorrected and were obtained in open capillary tubes in paraffin bath. TLC checking was done on glass plates coated with silica gel – G and spotting was done using iodine. IR spectra were recorded on NICOLET FT-IR instrument.[1]HNMR were taken at IISc Bangalore.

Method of preparation of Schiff Bases (I)[2-3]

To the equimolar mixture of 4- methoxy phenylamine (I) (0.1 mol) and aryl aldehyde (0.1 mol) in 25 ml of methanol and drops of glacial acetic acid was refluxed for a period of 3 to 4 hours cooled, and was poured into the cold water. The solid separated was filtered and the same was crystallized from methanol.

Method of synthesis of 1,5 diaryl imidazoles (II)[4]

To mixture of compound II (115 mmol), tosylmethyl isocyanide(172 mmol), anhydrous

potassium carbonate (229 mmol), methanol (40 ml) and Dioxane (16 ml) was refluxed for 2 to 4 hours. The solvent was removed and the residue was dissolved in dichloromethane/brine mixture. The layer was separated and the aqueous phase was extracted with dichloremethane. The combined organic phases were dried over magnesium sulphate and concentrated and the same was recrystallized with methanol.

Synthesis of 4-chloro 1,5-diaryl imidazoles (III)[4]

A mixture of compound III (86mmol), N-chlorosuccinamide (90mmol), and chloroform (35 ml) was refluxed for 18 hours. The solvent was removed and the residue was redissolved in dichloromethane and was washed with 1N HCl, 1N NaOH and brine. The organic phase was dried over anhydrous magnesium sulphate and was concentrated. The product was crystallized from alcohol.

Synthesis of 1H-imidazol-2-ylamino) phenol derivative(IV)

Compound IV (0.01 mmol), 4- phenoxy aniline of (0.01 mmol) in methanol (50 ml) and drops of hydrochloric acid was refluxed for a period of 8 to 10 hours. The refluxed product was cooled overnight in vaccum and condensed. The product was crystallized with alcohol.

RESULT AND DISCUSSION

The synthesized imidazolines derivatives compounds resemble to some of COX-II inhibitory agents like Celecoxib and Rofocoxib. Hence it was thought of carrying out Anti-inflammatory screening by carrageenan induced paw edema method by using water displacement plethysmography. As result, the screened compounds have shown good Anti-inflammatory activity.

The structures of all the synthesized compounds were established on the basis of MP, chemical tests, TLC, UV, IR, NMR.

PHARMACOLOGICAL STUDIES[8-9]

All the synthesized compounds were subjected to in vivo anti-inflammatory activity i.e carrageenan induced rat hind paw edema technique. Albino rats weighing 100-200 gram were used for the experiment and indomethacine taken as standard and surprisingly all the synthesized compounds shown very good anti-inflammatory activity.

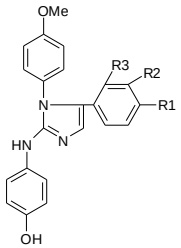
Below table shows the result of activity.

Anti Inflammatory Activity

S. No.	Drug (100mg/kg)	Mean Paw Oedema Volume (ml) ± SE			
		0 hr	1 hr	2 hr	3 hr
1.	Control	3.7100±0.0371	4.5900± 0.0911**	5.35 ± 0.0131	5.35 ± 0.0144
2.	Std. Indomethacine	3.62 ± 0.049	3.68 ±0.05514**	3.62 ± 0.0974**	3.65 ± 0.1252**
3.	COMP-1	3.64 ± 0.032	3.70 ±0.0325**	3.78 ± 0.0661**	3.79 ± 0.0454**
4.	COMP-2	3.57 ± 0.078	3.66 ±0.0606**	3.75 ±. 0632**	3.44 ± 0.0482**
5.	COMP-3	3.69 ± 0.029	3.98 ± 0.0694**	4.43 ± 0.0728**	4.38 ± 0.0723**
6.	COMP-4	4.34 ± 0.3312	4.70 ±0.1091^{NS}	4.76 ± 0.0652**	4.77 ± 0.0631**
7.	COMP-5	3.57 ± 0.1624	3.63 ±0.1411**	3.73 ± 0.1101**	3.86 ± 0.0702**
8	COMP-6	3.49 ± 0.0381	3.85 ±0.0385**	4.00± 0.05711**	3.81± 0.06125**

NA-P < 0.05 – Non significant, ** P < 0.01 – Significant, (ANOVA followed by Dunnet 't' test)

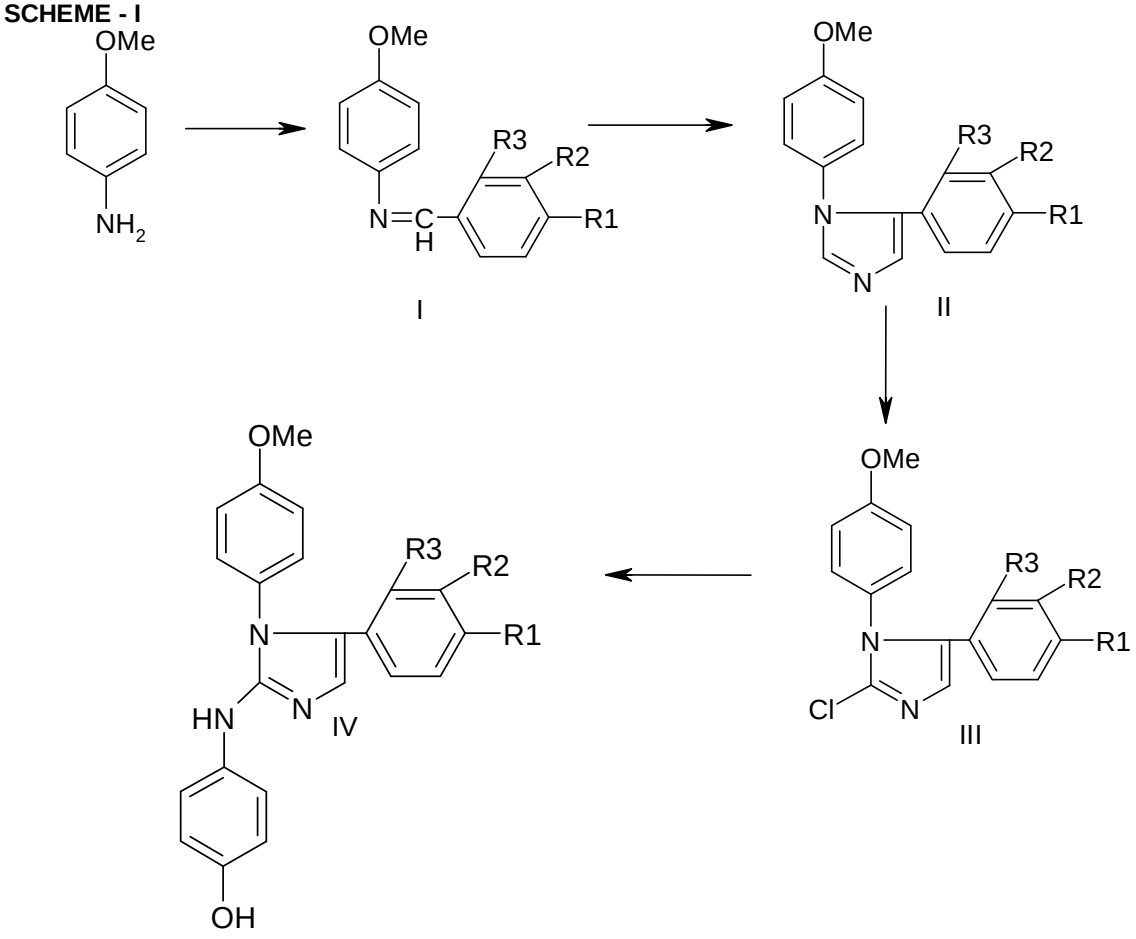
SPECTRAL DATA[6-7]



S. No.	Comp.	R1	R2	R3	% Yield	Molecular Formula	Molecular Weight
1	**Comp – I**	OH	H	H	69	$C_{22}H_{19}O_2N_3$	371
2	**Comp – II**	OCH_3	H	H	60	C23H23O4N3	387
3	**Comp – III**	OCH_3	OCH_3	H	58	$C_{24}H_{21}O_3N_3$	405
4	**Comp – IV**		H	H	55	$C_{24}H_{21}O_2N_4$	400
5	**Comp – V**	H	Cl	H	62	$C_{22}H_{18}O_2N_3Cl$	391.5
6	**Comp - VI**	H	Cl	H	55	$C_{22}H_{18}O_2N_3Cl$	391.5

Comp$_1$: IR (KBr) cm^{-1}: 2926 (NH Stretch, Aromatic Amino.), 3424 (OH Phenolic), 1349 (C-N Stretch.), 1200 (C-O Stretch.)
Comp$_2$: IR (KBr) cm^{-1}: 2915 (NH Stretch, Aromatic Amino.), 3403 (OH Phenolic), 11349 (C-N Stretch.), 1198 (C-O Stretch.)
Comp$_3$:IR (KBr) cm^{-1}: 2926 (NH Stretch, Aromatic Amino.), 3410 (OH Phenolic), 1349 (C-N Stretch.), 1242 (C-O Stretch.)
H^1 NMR (ð ppm): 3.132 (9 H, 3 (-OCH_3), 3.9 (1H, -NH Ar.), 6.5 (11H, Aromatic), 8.2 (1H, imidazole – NH).
Comp$_4$:IR (KBr) cm^{-1}: 2925 (NH Stretch, Aromatic Amino.), 3406 (OH Phenolic), 1349 (C-N Stretch.), 1237 (C-O Stretch.)
Comp$_5$:IR (KBr) cm^{-1}: 2931 (NH Stretch, Aromatic Amino.), 3425 (OH Phenolic), 1349 (C-N Stretch.), 1203 (C-O Stretch.)
Comp $_6$:IR (KBr) cm^{-1}: 2931 (NH Stretch, Aromatic Amino.), 3416 (OH Phenolic), 1349 (C-N Stretch.), 1202 (C-O Stretch.)

SCHEME - I



CONCLUSION

The compound could be synthesized from readly available p-methoxy aniline. The compounds were found to be active and shown good anti-inflammatory activity, considering this work is fruitful as it give some more new ideas for modification to design new drugs.

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