Nimesulide Based 1,2,4,5-Tetra Substituted Imidazole Derivative: Synthesis and Characterisation

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Chemical Abstract
Nimesulide a preferential “cyclooxygenase-2 inhibitor” is one of the well-known non-steroidal anti-inflammatory drugs that has been utilized to treat pain and other inflammatory diseases. Nimesulide was withdrawn from the market due to its hepatotoxicity which could be due to the presence of nitro group. Imidazoles represent an important class of bioactive molecules that shows a wide range of pharmacological activities besides anti-inflammatory activity. In our strategy to develop safer and potential anti-inflammatory molecules, we have decided to combine some of the structural features of nimesulide and imidazole in a single molecule. We have described the design and synthesis of nimesulide based 1,2,4,5-tetra substituted imidazole of potential biological significance via chemical modifications of a commonly used anti-inflammatory agent nimesulide. This derivative was prepared from nimesulide via a two-step process involving regio selective reduction of nimesulide followed by hetero cyclisation of reduced nimesulide in very 81% yield. The title compound nimesulide based 1,2,4,5-tetra substituted imidazole was synthesized in very good yield by reaction of benzil, benzaldehyde, ammonium acetate, and N-(4-amino-2-phenox phenyl) methane sulphonamide in acetic acid using multi-component strategy and molecular modification. The structure of the synthesized compound was confirmed by IR and H1 NMR spectral analysis.

Keywords: Nimesulide; Nimesulide based 1,2,4,5-tetra substituted imidazole; Molecular modification

Introduction
Nimesulide a preferential “cyclooxygenase-2 inhibitor” is one of the well-known non-steroidal anti-inflammatory drugs that have been utilized to treat pain and other inflammatory diseases. Nimesulide was withdrawn from the market due to its hepatotoxicity which was due to the presence of nitro group(=NO2) [1,2]. Imidazoles represent an important class of bioactive molecules that shows a wide range of pharmacological activities besides anti-inflammatory activity. In our strategy to develop safer and potential anti-inflammatory molecules, we have decided to modify the toxicophore and integrate some of the structural features of nimesulide and imidazole in a single molecule. Because of their common anti-inflammatory properties and our interest in nimesulide derivatives as potential anti-inflammatory agents, we decided to prepare a compound having structural features of nimesulide in a single molecule. We estimated that a combination of structural features of imidazole with nimesulide in a single molecule would provide novel agents possessing potent pharmacological activities. We report the synthesis nimesulide based 1,2,4,5-tetra substituted imidazole as hybrid molecule derived from nimesulide in very 81% yield from nimesulide via reducing its nitro group followed by hetero cyclisation using multicomponent strategy [3,4].
Synthetic scheme:

Synthesis of Nimesulide based 1,2,4,5-tetra substituted Imidazole

Materials and Methods

Synthetic procedure

0.016 moles of reduced nimesulide, 0.005 moles of benzil, 0.005 moles of benzaldehyde, 0.012 moles of ammonium Acetate, 0.174 moles of acetic acid were taken in a clean, dry round bottom flask fitted with a reflux condenser along with condenser pipes. The reaction mixture was heated on a magnetic stirrer at 970 RPM with a hot plate to reflux at 120 °C for about 6 hours. The progress of the reaction was monitored using ascending TLC technique. Excess acetic acid was distilled off and the reaction mixture was quenched into 100 mL of ice-cold water [5,6]. Crude 1,2,4,5 tetra substituted imidazole separated out as solid which was filtered at suction, washed with sodium bisulfite wash, cold water, dried, and recrystallized from suitable recrystallization technique.

Results and Discussions

Computational data of the title compound using Chem sketch, Mol inspiration, Pro Tox-II and Swiss ADME (Table 1 & 2).

Table 1: Table of characterization.

| Physical state                     | Amorphous solid |
|------------------------------------|-----------------|
| Color                              | Yellow          |
| Physical constant                  | M.P: 167 °C     |
| Theoretical yield                  | 2 Gms           |
| Practical yield                    | 1.62 Gms        |
| Percentage of yield                | 81              |
| Recrystallizing solvent            | Chloroform      |
| Mobile phase for TLC               | Chloroform and Ethyl acetate in the ratio 2:1 |
| R_f value                          | 0.86            |
| Molecular formula                  | C_{34}H_{27}N_{3}O_{3}S |
| Molecular weight                   | 557.66          |
| IR-spectral data                   | 2970,1444 (CH_{3}); 1346 (S=O); 1160(Ether); 968,765,694,835 (Benzene ring); 1346(C-N). |
| Elemental data:                    | C (73-23%) H (4.88%) N (7.54%) O (8.61%) S (5.75%) |

Table 2: Table of computational data.

|                     | Nimesulide | Nimesulide Based 1,2,4,5-Imidazole Derivative |
|---------------------|------------|---------------------------------------------|
| Structure           | ![Image]   | ![Image]                                    |
| Molar refractivity  | 76.32 ± 0.4 cm³ | 164.97 ± 0.5 cm³                           |
| Molar volume        | 212.3 ± 3.0 cm³ | 454.0 ± 7.0 cm³                             |
| Parachor            | 595.9 ± 4.0 cm³ | 120.47 ± 8.0 cm³                            |
| Index of refraction | 1.638 ± 0.02 | 1.646 ± 0.05                                |
| Polarizability      | 30.25 ± 0.5×10⁻²⁴cm³ | 65.40 ± 0.5×10⁻²⁴cm³                      |
| RDBE                | 11          | 25                                          |
### Conclusion

In conclusion, we have described the design and synthesis of nimesulide based 1,2,4,5-tetra substituted imidazole of potential biological significance via chemical modifications of a commonly used anti-inflammatory agent nimesulide. It was prepared from Nimesulide via a two-step process involving reduction of nimesulide followed by hetero cyclisation of reduced nimesulide in very 81% yield. Moreover, because of the lack of nitro group in the final molecule, it is expected to be free from the side effects of nimesulide such as hepatotoxicity which is due to nitro group. Overall, the present nimesulide-based imidazole framework appeared to be a useful template for the design and identification of novel and potential anti-inflammatory agents.

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### References

1. John H Gajewski (1965) Molecular Modification in Drug Design. Clinical Chemistry 11(5): 612.
2. Sandhya P, Jyoti M, Geetha Rani DP, Padmavathi VG, Sarbani P (2007) Chemical Modifications of Nimesulide. J Braz Chem Soc 18(2): 384-390.
3. Ghodsi MZ, Zeinab D, Monireh SN, Alireza B (2015) One-pot synthesis of 1,2,4,5-tetra substituted Imidazoles using sulfonic acid functionalized silica (SiO2-Pr-SO3H). Arabian Journal of Chemistry 8(5): 692-697.
4. Nascimento MVPS, Munhoz ACM, Theindl LC, Mohr ETB, Saleh N, et al. (2018) A novel tetrasubstituted imidazole as a prototype for the development of anti-inflammatory drugs. Inflammation 41(4): 1334-1348.
5. Banerjee P, Eckert OA, Schrey AK, Preisner R (2018) ProTox-II: a webserver for the prediction of toxicity of chemicals. Nucleic Acids Res 46(W1): W257-W263.
6. Antoine Daina, Olivier Michaelin, Vincent Zoete (2017) Swiss ADME: a free web tool to evaluate pharmacokinetics, drug-likeness and medicinal chemistry friendliness of small molecules 7: 42717.