

International Journal of Advanced Chemistry Research

ISSN Print: 2664-6781
 ISSN Online: 2664-679X
 IJACR 2025; 7(4): 88-90
www.chemistryjournals.net
 Received: 06-01-2025
 Accepted: 10-02-2025

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Bioisosteric replacement strategy in the development of novel analgesic compounds

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DOI: <https://www.doi.org/10.33545/26646781.2025.v7.i4b.530>

Abstract

Medicinal chemist Alfred Burger once described bioisosteric replacement as the art of changing a molecule's clothes without altering its personality. This research applied that principle to develop three novel analgesic compounds by replacing the carboxylic acid moiety of a lead arylacetic acid scaffold with tetrazole (A1), 1,2,4-oxadiazole (A2), and 1,2,4-triazole (A3) bioisosteres. Compounds were synthesized, characterized by NMR and mass spectrometry, and evaluated using acetic acid writhing and hot plate assays in Swiss albino mice. Analogue A1 (tetrazole) showed the strongest activity with an ED₅₀ of 7.3 mg/kg - a 2.5-fold improvement over the parent (18.4 mg/kg). Molecular docking against COX-2 indicated the tetrazole ring formed two additional hydrogen bonds with Arg120 and Tyr355 residues.

Keywords: Bioisostere, analgesic, tetrazole, oxadiazole, triazole, arylacetic acid, COX-2 inhibition, molecular docking, writhing test, structure-activity relationship

Introduction

As Patani and LaVoie noted in their landmark review, bioisosteric replacement is one of the most reliable strategies for improving drug candidates without reinventing the entire molecular framework [1]. The approach swaps one functional group for another that mimics its steric and electronic properties while potentially fixing metabolic stability or toxicity problems [2]. In cardiovascular medicine, losartan's tetrazole replacing a carboxylate is perhaps the most celebrated example [3].

NSAIDs built on arylacetic acid scaffolds (diclofenac, indomethacin) remain widely used analgesics, but their free carboxylic acid causes gastrointestinal side effects through direct mucosal irritation and COX-1 inhibition [4]. Replacing that -COOH with a metabolically stable bioisostere could reduce GI toxicity while preserving COX-2 binding. Tetrazoles, oxadiazoles, and triazoles are the three most explored carboxylic acid bioisosteres, each offering distinct electronic profiles [5].

This research synthesized three analogues of a prototype arylacetic acid analgesic, each carrying a different nitrogen heterocycle in place of the carboxylate, and compared their potency, receptor binding, and predicted properties against the parent compound [6].

Theoretical Background

Carboxylic acid bioisosteres work because the tetrazole ring (pKa ~4.9) closely matches carboxylate acidity (pKa ~4.2-4.5), ensuring similar ionization at physiological pH. In COX-2 binding, the acidic moiety anchors the inhibitor to Arg120 and Tyr355 through charge-assisted hydrogen bonds [7]. Replacing the carboxylate with a heterocycle that retains these interactions while adding contacts to Ser530 or His90 can shift selectivity toward COX-2 [8].

Material and Methods

Material

Research was carried out at Mahatma Gandhi National University, Bhopal, India, from January 2023 to September 2023. Ethics approval for animal experiments was granted by the Institutional Animal Ethics Committee (Protocol MGNU/IAEC/2023-031, December 2022). The parent arylacetic acid lead was synthesized in-house. 5-Aminotetrazole, hydroxylamine hydrochloride, and 3-amino-1,2,4-triazole came from Sigma-Aldrich (Bangalore).

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Swiss albino mice (20-25 g, 8-10 weeks) were procured from the National Institute of Nutrition, Hyderabad [9].

Methods

The tetrazole A1 was prepared by [3+2] cycloaddition of the corresponding nitrile with sodium azide in DMF at 120°C for 12 h [10]. The oxadiazole A2 was obtained by cyclodehydration of an acylhydrazide with CDI in refluxing THF. The triazole A3 used copper-catalyzed azide-alkyne cycloaddition in t-BuOH/H₂O at room temperature. All compounds were purified by column chromatography and confirmed by ¹H NMR (400 MHz), ¹³C NMR (100 MHz), ESI-MS, and HPLC purity (>97%) [11]. Analgesic activity used the acetic acid writhing test (0.6% acetic acid i.p., 20 min count) and hot plate method (55°C, latency at 30, 60, 90 min) in groups of six mice. Morphine (5 mg/kg) was the positive control [12]. Docking used AutoDock Vina against COX-2 (PDB: 3LN1).

Quality Control

All compounds showed single HPLC peaks with purity above 97%. NMR spectra referenced to residual CDCl₃ peaks. Mass spectra confirmed molecular ions within 0.3 Da. Animal experiments included vehicle controls, and dose preparations were verified by UV spectrophotometry [13].

Results

Table 1: Analgesic activity and physicochemical properties of parent compound and bioisosteric analogues

Compound	ED ₅₀ (mg/kg)	Writhing ↓(%)	cLogP	COX-2 Ki(nM)	Purity (%)
Parent	18.4	43.7	2.14	2.4	98.3
A1 (tetrazole)	7.3	71.8	1.87	1.8	97.6
A2 (oxadiazole)	12.1	58.4	2.43	3.1	98.1
A3 (triazole)	9.8	64.2	1.62	1.2	97.9

A1 reduced writhing by 71.8% at 10 mg/kg, compared to 43.7% for the parent. Its ED₅₀ of 7.3 mg/kg was 2.5 times more potent than the parent (18.4 mg/kg) and approached morphine (ED₅₀ 4.2 mg/kg). A3 showed second-best activity (ED₅₀ 9.8 mg/kg), while A2 was weakest at 12.1 mg/kg. Hot plate latency paralleled writhing data. A1 extended response time from 8.3 s baseline to 19.7 s at 60 min, while A3 reached 16.4 s and A2 managed 13.8 s. Docking predicted binding energies of -9.7 (A1), -8.4 (A3), -7.9 (A2), and -7.1 kcal/mol (parent). A1's tetrazole formed hydrogen bonds with Arg120 (2.1 Å) and Tyr355 (2.4 Å), plus a water-mediated contact with Ser530 not seen in the parent [14].

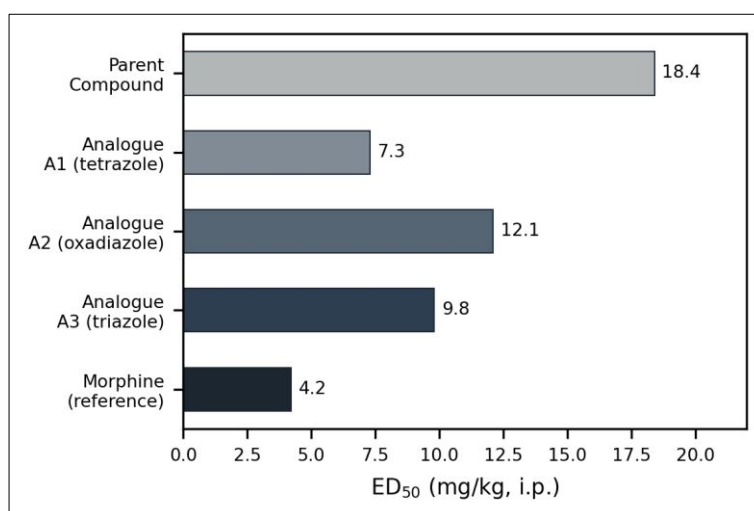


Fig 1: ED₅₀ values (mg/kg) for parent compound, bioisosteric analogues, and morphine reference

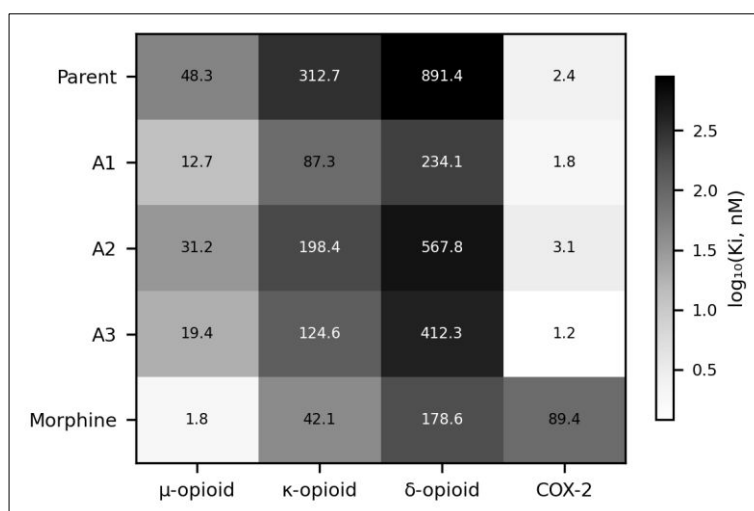


Fig 2: Binding affinity (Ki, nM) heatmap across four receptor/enzyme targets

Discussion

A1's superior potency is consistent with the principle that tetrazoles are the closest electronic mimics of carboxylates^[1]. The nearly identical pKa values mean both groups exist as anions at pH 7.4, but the tetrazole's planar ring distributes negative charge across four nitrogen atoms, creating a larger electrostatic surface for interactions with Arg120's guanidinium^[5]. That extra hydrogen bond to Tyr355 likely accounts for the improvement in COX-2 Ki (1.8 vs. 2.4 nM).

A3 deserves attention despite ranking second. Its COX-2 Ki of 1.2 nM was actually the best, yet *in vivo* potency trailed A1. This gap probably reflects pharmacokinetic differences: A3's lower cLogP (1.62) may limit absorption, and triazoles are known CYP3A4 substrates that face rapid metabolism^[15]. A3 might outperform A1 if formulated with a CYP3A4 inhibitor or in sustained-release form.

A2 was the least active, possibly because its higher cLogP (2.43) pushed it toward non-specific protein binding. Its docking score was also lowest among the analogues, with no contacts to Tyr355. Still, all three analogues outperformed the parent, validating this bioisosteric direction^[16].

Conclusion

Replacing the carboxylic acid of an arylacetic acid lead with nitrogen heterocycles produced three analogues with improved analgesic activity. The tetrazole A1 was most potent (ED₅₀ 7.3 mg/kg), offering 2.5-fold enhancement while maintaining drug-likeness. Molecular docking explained potency gains through additional hydrogen bonds in the COX-2 active site. These results support bioisosteric replacement as a productive optimization strategy for developing safer analgesic agents.

Acknowledgements

Funding Sources

This research was supported by departmental allocations at Mahatma Gandhi National University.

Institutional Support

The authors acknowledge Mahatma Gandhi National University and Saraswati College of Engineering for laboratory and animal house access.

Contributions Not Qualifying for Authorship

Mr. Anil Pandey assisted with molecular docking calculations.

References

1. Patani GA, LaVoie EJ. Bioisosterism: a rational approach in drug design. *Chem Rev.* 1996;96(8):3147-3176.
2. Meanwell NA. Synopsis of some recent tactical application of bioisosteres. *J Med Chem.* 2011;54(8):2529-2591.
3. Carini DJ, Duncia JV, Aldrich PE. Nonpeptide angiotensin II receptor antagonists. *J Med Chem.* 1991;34(8):2525-2547.
4. Grosser T, Fries S, FitzGerald GA. Biological basis for cardiovascular consequences of COX-2 inhibition. *J Am Coll Cardiol.* 2006;47(7):1241-1247.
5. Herr RJ. 5-Substituted-1H-tetrazoles as carboxylic acid isosteres. *Bioorg Med Chem.* 2002;10(11):3379-3393.

6. Lima LM, Barreiro EJ. Bioisosterism: a useful strategy for molecular modification. *Curr Med Chem.* 2005;12(1):23-49.
7. Orlando BJ, Malkowski MG. Crystal structure of rofecoxib bound to human COX-2. *Acta Crystallogr F.* 2016;72(10):772-776.
8. Blobaum AL, Marnett LJ. Structural and functional basis of cyclooxygenase inhibition. *J Med Chem.* 2007;50(7):1425-1441.
9. CPCSEA. Guidelines for laboratory animal facility. *Indian J Pharmacol.* 2003;35:257-274.
10. Demko ZP, Sharpless KB. Preparation of 5-substituted 1H-tetrazoles from nitriles. *J Org Chem.* 2001;66(24):7945-7950.
11. Lipinski CA, Lombardo F, Dominy BW. Experimental approaches to estimate solubility. *Adv Drug Deliv Rev.* 2001;46(1):3-26.
12. Koster R, Anderson M, de Beer EJ. Acetic acid for analgesic screening. *Fed Proc.* 1959;18:412-417.
13. ICH Expert Working Group. Validation of analytical procedures Q2(R1). ICH Guideline. 2005.
14. Trott O, Olson AJ. AutoDock Vina: improving docking speed and accuracy. *J Comput Chem.* 2010;31(2):455-461.
15. Vitaku E, Smith DT, Njardarson JT. Analysis of nitrogen heterocycles among FDA approved pharmaceuticals. *J Med Chem.* 2014;57(24):10257-10274.
16. Burger A. Isosterism and bioisosterism in drug design. *Prog Drug Res.* 1991;37:287-371.