



Synthesis of new derivatives of 9-(2-pyridyl)-3-aryl(arylalkyl)-2,4,5(9H)trioxo-7,8-dihydroimidazo[1,2-a][1,3,5]triazepine

MARZENA RZADKOWSKA^{1*}, ELZBIETA SZACON¹, MARIA ZUN²

¹ Chair and Department of Synthesis and Chemical Technology of Pharmaceutical Substances with Computer Modeling Unit, Faculty of Pharmacy with Division of Medical Analytics, Medical University of Lublin, Chodzki 4a, 20-093 Lublin, Poland

² Chair and Department of Applied Pharmacy, Faculty of Pharmacy, Medical University of Lublin, Chodzki 1, 20-093 Lublin, Poland

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ABSTRACT

A series of new derivatives of 9-(2-pyridyl)-3-aryl(arylalkyl)-2,4,5(9H)trioxo-7,8-dihydroimidazo[1,2-a][1,3,5] triazepine was obtained by condensation of 1-[1-(2-pyridyl)imidazolidine-2-ylidene]-3-aryl(arylalkyl)ureas) with diethyl oxalic acid ester. Considering the structure of the obtained compounds, it can be expected that these compounds can reveal pharmacological activity.

INTRODUCTION

In the recent years at the Department of Synthesis and Technology of Drugs, a number of fused derivatives of triazepine has been synthesized [11,13].

The synthetic derivatives of triazepine form various and important group of medicines. In the search for new structures with potential pharmacological activity, a set of novel imidazo[1,2-a][1,3,5]triazepines has been obtained. Some known derivatives of imidazotriazepine show activity as muscle relaxants [1], the others have antifungal [8], anti-diabetic [3,9,10], antimicrobial [2,4,5], antiviral [7,14], anticancer [7] and analgesic [6] properties. This heterocyclic system has been obtained by us in a two-step reaction. It seemed worthwhile to synthesize new imidazo[1,2-a][1,3,5]triazepine derivatives to estimate their pharmacological activity.

MATERIALS AND METHODS

General procedure for the synthesis of 9-(2-pyridyl)-3-aryl(arylalkyl)-2,4,5(9H)-trioxo-7,8-dihydroimidazo[1,2-a][1,3,5] triazepines

Diethyl oxalate acid ester (0,01 mole) was added to 1-[1-(2-pyridyl)imidazolidine-2-ylidene]-3-aryl(arylalkyl)ureas) (0.01 mole) dissolved in 50 cm³ of DMF. The mixture was heated under reflux for 10-12h. The solvent was evaporated under reduced pressure to ca. a half its volume. The precipitate was filtered off and finally recrystallized.

Corresponding author

* e-mail: marzena.rzadkowska@umlub.pl

RESULTS AND DISCUSSION

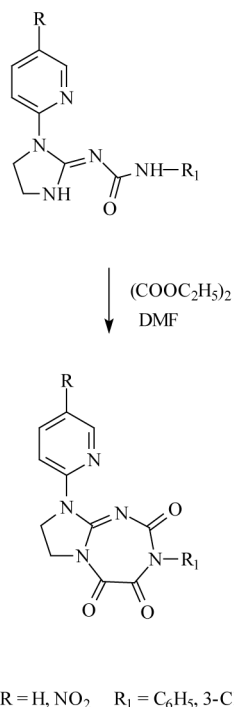
New 9-(2-pyridyl)-3-aryl(arylalkyl)-2,4,5(9H)-trioxo-7,8-dihydroimidazo[1,2-a][1,3,5]triazepines were received as a result of condensation of 1-[1-(2-pyridyl)imidazolidine-2-ylidene]-3-aryl(arylalkyl)ureas [6,12] with diethyl oxalic acid ester. The reaction was conducted in the boiling temperature of the solvent. The reaction sequence leading to the formation of small molecules (I-V) is outlined in Scheme 1.

Melting points were determined on a Boetius apparatus and given uncorrected. The ¹H NMR spectra were recorded on AVANCE 300 MHz spectrometers stiffy Bruker in DMSO-d₆ as an internal standard. Elemental analyses were performed on a Perkin-Elmer analyzer. All the compounds were recrystallized from propan-2-ol. Chemicals for synthesis were purchased from Merck Co or Fluka Lab. and used without purification. Purity of the compounds was checked by thin layer chromatography (TLC). TLC was performed on commercial Merck SiO₂ plates with chloroform-methanol (10:2) solvent system and visualization under UV light at 254 nm.

The physical data of new compounds are shown in Table 1, whereas their spectral data are provided underneath Table 1.

¹H NMR (DMSO-d₆); (ppm) for:

Comp.I: 6.65-6.90 (m.9H.CH_{arom}); 3.52-3.80 (m.4H.2CH₂),
Comp.III: 7.50-7.85 (m.8H.CH_{arom}); 3.33-3.60 (m.4H.2CH₂);
Comp.IV: 7.10-7.30 (m.7H.CH_{arom}); 3.68-3.90 (m.4H.2CH₂),
Comp.V: 7.11-7.16 (m.9H.CH_{arom}); 3.52-3.80 (m.4H.2CH₂);
2.29-2.41 (m.4H.2CH₂)



Scheme 1. Synthetic route to small molecules (I-V) under study

Table 1. The physical and spectral data of new compounds

Comp.	R R ₁	Formula (mol.wght.)	M.p. (°C) Yield (%)	Analyses (calcd/found)			
				% C	% H	% Cl	% N
I	H C ₆ H ₅	C ₁₇ H ₁₃ N ₅ O ₃ 367.33	235-37 36	55.59	3.57		21.78
				55.53	3.60		21.60
II	4-NO ₂ C ₆ H ₅	C ₁₇ H ₁₂ N ₅ O ₅ 380.33	253-55 40	53.67	3.18		23.00
				53.59	3.16		23.02
III	H 3-ClC ₆ H ₄	C ₁₇ H ₁₂ ClN ₅ O ₃ 369.78	234-36 42	55.22	3.27	9.59	21.63
				55.24	3.27	9.67	21.66
IV	4-NO ₂ 3-ClC ₆ H ₄	C ₁₇ H ₁₁ ClN ₅ O ₅ 414.48	203-05 32	49.26	2.68	8.55	20.28
				49.20	2.67	8.58	20.00
V	H CH ₂ CH ₂ C ₆ H ₅	C ₁₉ H ₁₇ N ₅ O 363.38	218-20 40	62.80	4.72		19.27
				62.82	4.77		19.20

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REFERENCES

- Cale A; Gero T: 2-(2-substituted aminoethyl)-1,4-dialkyl-3,4-dihydro-1H-[1,3,5]triazepino[3,2-a] benzimidazol-5(2H)-ones as muscle relaxants. US Patent 5 109 013.1990
- Clivio P; Peyrane F: New 1,3,5-triazepine-2,4-dione derivatives useful as antiviral and anticancer agents.e.g. for treatment of HIV infection and leucemia. US Patent 2006 4 275 057.
- Deohate P.P; Deohate Jyoti P., Berad B.N.: Novel benzo-1,3,6 triazepines:Synthesis antimicrobial activity. *Asian Journal of Chemistry* 16 (2), 773, 2004
- Deohate P.P; Berad B.N.: Synthesis of some novel benzo 1,3,6-thiadiazepines.Their antimicrobial activity and isomerization to benzo-1,3,5-triazepines. *Oriental J Chem.* 20(1), 139, 2004
- Doleschall G; Hornyak G.; Simig G. et al: Condensed 1,3,5-triazepines-II: the synthesis of 2,3-dihydro-1H-imidazo [1,2-a] [1,3,5]benzotriazepin-5(6H)-ones and thionones.: *Tetrahedron* 32(1), 57, 1976
- Flieger J.,Czajkowska-Żelazko A.,Rządowska M.,Szacoń E.,Matosiuk M.: Usefulness of reversed-phase HPLC enriched with room temperature imidazolium based ionic liquids for lipophilicity determination of the newly synthesized analgesic active urea derivatives. *J Pharm Biomed Anal.* 66, 58, 2012
- Hosmane RS: Ring-expanded (Fat) nucleosides as broad-spectrum anticancer and antiviral agents.; *Current Topics in Medicinal Chemistry* 2(10), 1093, 2002
- Mahran MA, El-Sayed OA, Fahmy HT, Ashour EA: Synthesis of some novel perhydrotriazepine-3,6-diones of potential antifungal activity. *J Pharm Sci.* 10(2), 133, 1996
- Ruggiero D, Wiernsperger N, Paterean G, Moinet G: Preparation of triazepinones for diabetes and diabetic complications. WO Patent. 9 936 396, 1999
- Ruggiero-Lopez D, Lecomte M, Moinet G et al.: Reaction of metformin with dicarbonyl compounds. Possible implication in the inhibition of advanced glycation and product formation. *Biochemical Pharmacology.* 58(11), 1765, 1999
- Rządowska M, Szacoń E, Matosiuk D: Synthesis of new derivatives of 9-aryl 3-ethoxycarbonylmethyl-2,4,5(9H)trioxo-7,8-dihydroimidazo[1,2-a][1,3,5]triazepine. *Curr Issues Pharm Med Sci.* 26(1), 12, 2012
- Szacoń E, Rządowska M, Matosiuk D: Synthesis of new derivatives of 1-[1-(2-pyridyl)imidazolidine-2-ylidene]-3-aryl(arylalkyl)ureas. *Curr Issues Pharm Med Sci.* 25(4), 499, 2012
- Szacoń E, Rządowska M, Matosiuk D: Synthesis of new derivatives of 9-aryl-2,5(9H)-dioxo-2,3,4,5,7,8-hexahydroimidazo[1,2-a][1,3,5] triazepine. *Ann. UMCS Sec. DDD* 22(1), 53, 2009
- Zhang N, Chen H M, Koch V, Schmitz H et al.: Ring-expanded nucleoside and nucleoside analogues exhibit potent in vitro activity, against Flaviviridae NT Pases Helicases including those of the West Nile virus hepatitis C virus and Japanese encephalis virus. *J Med Chem.* 46(19), 4149, 2003