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A facile microwave-assisted synthesis of 8,9-cycloalkathieno[3,2-*e*][1,2,4]triazolo[1,5-*c*]pyrimidin-5(6*H*)-ones

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Abstract. A new series of fused thieno[3,2-*e*][1,2,4]triazolo[1,5-*c*]pyrimidinones was synthesized by condensation of ethyl-3-cyano-4,5,6,7-tetrahydrobenzo[*b*]thiophene-2-yl carbamate with aryl acid hydrazides in quantitative yields using a facile, one-pot procedure under microwave-assisted conditions.

Keywords. Microwave-irradiation; pyrimidinones; 1,2,4-triazole; aryl hydrazides; condensation.

1. Introduction

Asthma and chronic obstructive pulmonary disease (COPD) are prevalent inflammatory disorders of the lung and are poorly managed.[1] Available antiasthmatic agents such as anticholinergic agents, β_2 selective adrenergic agonists, methyl xanthines, antihistamines, mast cell stabilizers and corticosteroids are inadequately effective and some are suitable only for symptomatic relief and most of them exhibit undesirable side effects.[2] This necessitates further investigations in this field to develop potent clinical candidates. Recent trends in the development of new antiasthmatic agents include various agents such as adenosine receptor (ARs) antagonists, isoenzyme selective phosphodiesterase 4 (PDE4) inhibitors, inhibitors of the biosynthesis of interleukin-4 (IL-4) and IL-4 antagonists, lipoxygenase (LOX) and leukotriene (LT) inhibitors, thromboxane (TX) A_2 receptor antagonists, potassium channel openers and monoclonal antibodies.[3,4] It has been observed that adenosine plays an important role in mediating bronchial constriction, pulmonary inflammation and airway remodelling by interacting with its different G-protein coupled receptors: A_1, A_{2A}, A_{2B} and A_3 ARs. These receptors are implicated in a number of inflammatory cell types including mast cells, eosinophils, lymphocytes, neutrophils and macrophages which are expressed in lungs and are found to be important in the pathophysiology of asthma.[5] Hence they are considered to be important targets for new drug development for asthma.

Over the past decade, a number of potent and selective AR agonists and antagonists, of various structures, including xanthines and non-xanthines, have been developed[6,7] but relatively few compounds entered clinical trials[1,8–10] (table 1). This could be due to their poor pharmacokinetic profile, including low water solubility[8] and/or low CNS penetration. As a consequence, a lot of interest has been generated in recent years to find ligands of ARs with high degree of selectivity. A large number of studies are aimed at designing new ligands which are free from undesirable side effects.[11]

Among the various classes of heterocyclic compounds, a wide variety of fused pyrimidines such as pyrazolo-triazolo-pyrimidine, triazolo[1,5-*c*]quinazoline, triazolo[4,3-*a*]quinoxaline and imidazo[4,5-*c*]quinoline derivatives have been reported as selective

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Table 1. Adenosine receptor agonists and antagonists in clinical development for asthma and/or COPD.

S. No.	Drug name	Molecular targets	Clinical indication	Status
1.	EPI-2010 (EpiGenesis Pharmaceuticals)	Antisense oligonucleotide of A_1 AR	Inhibition of BHR and bronchodilatation	Discontinued
2.	UK-432,097 (Pfizer)	A_{2A} AR agonist	Anti-inflammation	Discontinued
3.	GW328267 (GSK)	A_{2A} AR agonist	Anti-inflammation	Discontinued
4.	CVT-6883 (CV Therapeutics)	A_{2B} AR antagonist	Inhibition of BHR and anti-inflammation	Phase 2
5.	QAF 805 (Novartis)	Mixed A_{2B}/A_3 AR antagonist	Inhibition of BHR and anti-inflammation	Phase 1b

antagonists for A_{2A} ARs.[12–17] Furthermore, inclusion of thienopyrimidine nucleus within a tetracyclic system afforded a large number of bioactive derivatives.[18] Recently a new series of triazolothienopyrimidines has been reported[11] from these laboratories as adenosine A_1 receptor antagonists with micromolar potencies. The encouraging results prompted us to design and synthesize new derivatives of triazolothienopyrimidines. Hence a facile method has been attempted using microwave-assisted synthesis of 8,9-cycloalkathieno [3,2-*e*][1,2,4]triazolo[1,5-*c*]pyrimidin-5(6*H*)-ones (**4**) by incorporating a substituted triazole ring with tetrahydrobenzothienopyrimidine in one framework. To achieve the synthesis of designed molecules (**4**), we adopted a route through an appropriate carbamate (**2**). When we completed their synthesis successfully, it was interesting to learn that an Ukrenian group came out with a different approach for the synthesis of related compounds.[19] We ascertained our data and interacted with them and it was observed that our method is comparatively easier and facile. The salient features of the investigated reaction under microwave-assisted conditions are enhanced reaction rates, greater selectivity, and ease of the experimental manipulation leading to an efficient and cost effective pathway to several synthetically useful compounds. The synthesis of target compounds appears to be an area of intense investigation as several related molecules with a broad range of activities have been reported recently.[19–23]

2. Experimental

2.1 *Materials, methods and instruments*

Reactions were routinely monitored by thin layer chromatography (TLC) on silica gel (pre-coated F_{254} Merck plates) and visualized the products under UV light (254 nm). ^{1}H NMR spectra were determined in $CDCl_3$ or DMSO-d_6 solutions with a Bruker Avance II 400 MHz spectrometer and signals recorded in parts per million (δ) downfield from tetramethylsilane as internal standard, and *J* values are given in Hz. IR spectra were recorded on Perkin Elmer FT-IR Spectrometer (Spectrum RX I) using KBr pellet technique. The elemental analyses were performed using Thermo EA 2110 series. Melting points were recorded in open capillaries on LABINDIA melting point apparatus and were uncorrected. Mass spectra (ESI) were recorded on Waters Micromass Q-TOF Micro.

2.2 *Preparation of ethyl 3-cyano-4,5,6,7-tetrahydrobenzo[b]thiophen-2-ylcarbamate* **(2)**

2.2a *Method A:* A suspension of **1** (5·28 g, 29·7 mmol) in ethyl chloroformate (14·1 ml, 148 mmol) was heated under microwave irradiation at 560 W for 5 min. The excess ethyl chloroformate was distilled off and toluene (9·6 ml) was added. Slow addition of cyclohexane in cold conditions induced crystallization. The resulting solid was collected by filtration and rinsed with cyclohexane. Drying under vacuum afforded compound **2**; yield 90%; mp 109–110°C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1·32–1·36 (*t*, 3H, $-CH_3$), 1·73–1·86 (*m*, 4H, $-(CH_2)_2-$), 2·55–2·62 (*m*, 4H, $-(CH_2)_2-$), 4·26–4·32 (*q*, 2H, $-OCH_2-$), 7·69 (*br s*, 1H, −NH−) ppm. IR (KBr): 3398·6, 3232·5, 2931·2, 2214·7, 1734·1, 1560·0, 1234·7 cm^{-1}. ESI-MS (*m/z*; %) = 273·5 (M^++Na^+; 15), 251·3 (M^++1; 30). Anal. Calcd. (%) for $C_{12}H_{14}N_2O_2S$: C, 57·58; H, 5·64; N, 11.19. Found (%): C, 57·36; H, 5·68; N, 11·37.

2.2b *Method B:* A suspension of **1** (5·28 g, 29·7 mmol) in ethyl chloroformate (14·1 ml, 148 mmol) was heated under reflux for 5 h. The excess ethyl chloroformate was distilled off and toluene (9·6 ml) was added. Slow addition of cyclohexane in cold conditions induced crystallization. The resulting solid was collected by

filtration and rinsed with cyclohexane. Drying under vacuum afforded compound **2**; yield 72%

2.3 *Preparation of 8,9-cycloalkathieno[3,2-e][1,2,4] triazolo[1,5-c]pyrimidin-5(6H)-ones* **(4a–d)**

2.3a *Method A:* Ethyl 3-cyano-4,5,6,7-tetrahydrobenzo [*b*]thiophen-2-ylcarbamate (**2**) (15·0 mmol) and aryl acid hydrazides (**3**) (15·0 mmol) were taken in DMF (10·0 ml). The resulting mixture was heated under microwave irradiation at 560W for 15–40 min. It was cooled to temperature below 100°C and added slowly to the crushed ice. The separated solid was collected by filtration and washed with water and 2-propanol. Drying in vacuum afforded the title compounds.

2.3b *Method B:* To a solution of ethyl 3-cyano-4,5,6,7-tetrahydrobenzo[*b*]thiophen-2-ylcarbamate **(2)** (15·0 mmol) in DMF (17·0 ml) was added aryl acid hydrazides (**3**) (15·0 mmol). The resulting mixture was heated at 120°C for 12–24 h under nitrogen-atmosphere. It was cooled to temperature below 100°C and added slowly to the crushed ice. The solid was collected by filtration and washed with water and 2-propanol. Drying in vacuum afforded the title compounds.

2.4 *2-Phenyl-8,9,10,11-tetrahydro[1]benzothieno[3,2-e] [1,2,4]triazolo[1,5-c]pyrimidin-5(6H)-one (***4a***, table 2, entry 1)*

^{1}H NMR (400 MHz, DMSO-d_6): δ = 1·85–1·86 (*m*, 4H, $-(CH_2)_2-$), 2·67–2·69 (*m*, 2H, $-CH_2-$), 3·03–3·04 (*m*, 2H, $-CH_2-$), 7·38–7·43 (*m*, 3H, Ar–H), 8·25–8·28 (*m*, 2H, Ar–H), 12·74 (*br s*, 1H, –NH–) ppm. ^{13}C NMR (100 MHz, DMSO-d_6): δ = 22·11, 23·25, 24·56, 25·12, 110·16, 127·41, 128·71, 128·74, 129·38, 130·36, 130·38, 143·00, 144·55, 151·52, and 163·67 ppm. IR (KBr): 2934·4, 1713·2, 1600·7, 1523·2, 1443·8, 747·7 cm^{-1}. ESI-MS (*m/z*; %) = 345·4 (M^++Na^+; 11) 323·4 (M^++1; 100). Anal. Calcd. (%) for $C_{17}H_{14}N_4OS$: C, 63·33; H, 4·38; N, 17·38. Found (%): C, 63·0; H, 4·28; N, 17·58.

2.5 *2-(4-Nitrophenyl)-8,9,10,11-tetrahydro[1] benzothieno[3,2-e][1,2,4]triazolo[1,5-c]pyri- midin-5 (6H)-one (***4b***, table 2, entry 2)*

^{1}H NMR (400 MHz, DMSO-d_6): δ = 1·93–1·95 (*m*, 4H, $-(CH_2)_2-$), 2·77 (*m*, 2H, $-CH_2-$), 3·08 (*m*, 2H, $-CH_2-$), 8·33–8·35 (*d*, 2H, *J* = 8·8 Hz, Ar–H), 8·50–8·52 (*d*, 2H, *J* = 8·8 Hz, Ar–H), 13·10 (*br s*, 1H, –NH–) ppm. ESI-MS (*m/z*; %) = 390·4 (M^++Na^+; 9), 368·2 (M^++1; 19). Anal. Calcd (%) for $C_{17}H_{13}N_5O_3S$: C, 55·58; H, 3·57; N, 19·06. Found (%): C, 55·45; H, 3·78; N, 19·26.

2.6 *2-(2-Hydroxyphenyl)-8,9,10,11-tetrahydro[1] benzothieno[3,2-e][1,2,4]triazolo[1,5-c] pyrimidin-5 (6H)-one (***4c***, table 2, entry 3)*

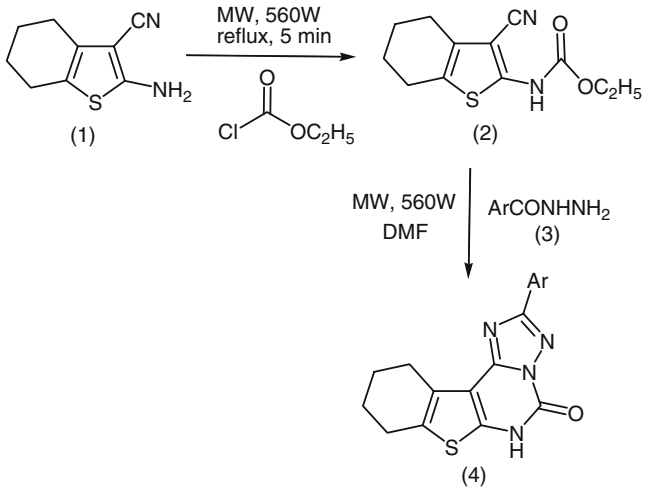
^{1}H NMR (400 MHz, DMSO-d_6): δ = 1·94 (*m*, 4H, $-(CH_2)_2-$), 2·77 (*m*, 2H, $-CH_2-$), 3·36 (*m*, 2H, $-CH_2-$), 6·95–6·99 (*t*, 1H, *J* = 7·6, 7·2 Hz, Ar–H), 7·01–7·03 (*d*, 1H, *J* = 8·0 Hz, Ar–H), 7·35–7·39 (*t*, 1H, *J* = 8·0, 7·2 Hz, Ar–H), 8·27–8·29 (*d*, 1H, *J* = 7·6 Hz, Ar–H), 11·13 (*s*, 1H, –OH), 13·10 (*br s*, 1H, –NH–) ppm. ESI-MS (*m/z*; %) = 361·3 (M^++Na^+; 11), 339·4 (M^++1; 14). Anal. Calcd (%) for $C_{17}H_{14}N_4O_2S$: C, 60·34; H, 4·17; N, 16·56. Found (%): C, 60·56; H, 4·01; N, 16·79.

2.7 *2-(2-Chlorophenyl)-8,9,10,11-tetrahydro[1] benzothieno[3,2-e][1,2,4]triazolo[1,5-c] pyrimidin-5 (6H)-one* (**4d***, table 2, entry 4)*

^{1}H NMR (400 MHz, DMSO-d_6): δ = 1·87–1·92 (*m*, 4H, $-(CH_2)_2-$), 2·74–2·75 (*m*, 2H, $-CH_2-$), 3·01–3·02 (*m*, 2H, $-CH_2-$), 7·41–7·49 (*m*, 2H, Ar –H), 7·54–7·56 (*dd*, 1H, *J* = 7·6, 7·2 Hz, Ar–H), 7·98–8·00 (*dd*, 1H, *J* = 7·6, 7·2 Hz, Ar–H), 13·01 (*br s*, 1H, –NH–) ppm. ESI-MS (*m/z*; %) = 381·3 (M^++Na^++2; 29), 379·3(M^++Na^+; 78), 359·3 (M^++2; 12), 357·3 (M^++1; 30). Anal. Calcd (%) for $C_{17}H_{13}ClN_4OS$: C, 57·22; H, 3·67; N, 15·70. Found (%): C, 57·52; H, 3·89; N, 15·95.

3. Results and discussion

The designed molecules fused thieno[3,2-*e*][1,2,4] triazolo[1,5-*c*]pyrimidinone derivatives **4a–d** were synthesized (scheme 1) starting from 2-amino-4,5,6,7-tetrahydrobenzo[*b*]thiophen-3-carbonitrile (**1**), which in turn was prepared following the well-known Gewald process.[24] Heating of **1** in excess of ethyl chloroformate gave ethyl-3-cyano-4,5,6,7-tetrahydrobenzo[*b*] thiophene-2-ylcarbamate (**2**) quantitatively.[25] Compound **2** was characterized based on a typical nitrile (C≡N) absorption band at 2214·7 cm^{-1}, a strong signal at 1734·1 cm^{-1} of the carbonyl group and an absorption band at 1560·0 cm^{-1} may be due to the ν (N–H) of ethyl carbamate. Further, prominent triplet signal at δ



Scheme 1. Synthesis of 8,9-cycloalkathieno[3,2-e][1,2,4] triazolo[1,5-c]pyrimidin-5(6H)-ones.

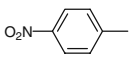
1·32–1·36 ppm and a quartet signal at δ 4·26–4·32 ppm of ethoxy protons and a broad singlet of NH at δ 7·69 ppm in ^{1}H NMR confirmed the presence of ethyl carbamate group as the expected absorption pattern of carbamates.[26] Title compounds (**4a–d**) were synthesized in good yields by irradiating compounds **2** and **3**[27,28] in dimethylformamide at 560W. The disappearance of nitrile (C≡N) stretch and appearance of absorption band at 1600·7 cm^{-1} related to the ν (C=N) stretch of triazole in IR and multiplet signals corresponding to aromatic protons at δ 7·38–7·43 ppm and 8·25–8·28 ppm and a broad singlet for NH proton of cyclic amide at δ 12·74 ppm in ^{1}H NMR confirmed the formation of title compounds (**4a–d).** Being a chlorinated compound **4d** exhibited the molecular ion or other halogenated fragments with the appropriate isotopic abundances in its mass spectrum. These compounds were also synthesized by conventional methods by treating **2** with aryl hydrazides (**3**) in DMF under nitrogen-atmosphere at 120°C for a comparative study.

Under classical heating conditions, these reactions have certain disadvantages like long reaction times (12–24 h), high energy consumption and the need for large amounts of solvents for work up and purification. The MW-assisted reactions were carried out using a Catalyst Microwave Reactor, under constant irradiation power and by varying the temperature (the so-called 'power control'). The best results were obtained when we used 80% of the full power of the magnetron (560 W). The details of the optimized conditions employed, under MW irradiation as well as under classical heating are presented in table 2. A comparative analysis of the data obtained leads to the conclusion that the use of MW resulted in a remarkable acceleration of the reactions, with the reaction times decreasing dramatically, from hours to minutes (15 to 40 min). While optimizing the conditions, it was interesting to note that the reactions could be carried out at considerably lower temperatures (in the most cases by 10 to 30°C). It was also of interest that, in some cases, under MW irradiation the yields were substantially higher (by almost 30%).

4. Conclusion

A series of thieno[3,2-*e*][1,2,4]triazolo[1,5-*c*]pyrimidinone derivatives **4a–d** was synthesized by employing innovative synthetic methods. We report here a

Table 2 Comparative data of conventional and microwave-assited synthesis of compounds **4a–d**.

Entry	Ar	Product*	Microwave-assisted (method-A)		Conventional (method-B)	
			Time (min) at 560 W	% Yield	Time (h)	% Yield
1		**4a**	29	72.8	19	41.3
2		**4b**	20	80.5	16	59.3
3		**4c**	40	65.6	24	39.6
4		**4d**	15	66.2	12	39.3

*These compounds were found to have melting points above 290ºC. The exact temperature could not be recorded

comparative study of their syntheses under microwave irradiation and by classical heating in solvent. A fast, general, environment-friendly, and facile method under microwave irradiation is presented. The microwave irradiation provided a remarkable rate of acceleration for the reaction, and the reaction time decreased dramatically and in some cases (under MW irradiation) the yields are also substantially higher. Efforts are currently underway to optimize the lead structure and the results of which will be the basis of our future research endeavour.

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