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Microwave-based synthesis of novel thienopyrimidine bioisosteres of gefitinib

Manisha S. Phoujdar [a], Muthu K. Kathiravan [b], Jitender B. Bariwal [c], Anamik K. Shah [c], Kishor S. Jain [a,*]

[a] *Sinhgad College of Pharmacy, Pharmaceutical Chemistry, S. No. 44/1, Vadgaon (BK), Sinhgad Road, Pune 411 041, India*
[b] *Poona College of Pharmacy, Pune 411 038, India*
[c] *Department of Chemistry, Saurashtra University, Rajkot 360 005, India*

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Abstract

A series of novel 2-unsubstituted 4-(substituted)anilinothieno[2,3-*d*]pyrimidines is synthesized through the chlorination of the corresponding 2-unsubstituted-thieno[2,3-*d*]-pyrimidin-4-ones, followed by the nucleophilic displacement of the 4-Cl group of 9, with a variety of anilines. All four steps of this synthesis involve microwave irradiation (MWI) and the entire synthesis requires only 2 h.

Keywords: Thieno[2,3-*d*]pyrimidines; MWI; Library synthesis

1. Introduction

Several tyrosine kinase inhibitors such as gefitinib[1] (Iressa®) **1**, erlotinib[2] (Tarceva®) **2**, lapatinib[3] **3** and canertinib[4] **4** have been found to exhibit effective antitumour activity. Bioisosterism between benzene and thiophene is well known and widely documented.[5] Based on this, Munchhof et al.[6] reported the design and structure activity relationship (SAR) of the bioisosteric thieno[3,2-*b*]pyrimidines **5**, as selective VEGFR-2 kinase inhibitors. This prompted us to explore the synthesis of the isomeric 4-anilino-2-unsubstituted-5,6-disubstituted-thieno[2,3-*d*]pyrimidines **6** for the evaluation of their antitumour activity (Fig. 1).

We initiated this study with the goal of expanding the efficiency of our recently reported[7] methodology for the synthesis of 2-amino-3-carbethoxy-4,5-disubstituted thiophene by microwave irradiation and to prepare chemical libraries by further compound functionalization. We envisioned that a focused library of analogues of **6** would provide interesting SAR data and allow us to analyze and improve the anticancer activity of this scaffold.

To meet the requirements of enhancing drug-like library synthesis, we herein report the synthesis of the biologically significant thienopyrimidine nucleus using microwave-assisted organic synthesis (MAOS) which has evolved in recent years as an important technique in Green chemistry.[8] Though having the major drawback of not being suitable for scale-up to bulk quantities, it offers the advantages of being efficient and rapid and thus finds great utility as a tool in new drug discovery research (NDDR) for the high throughput automated parallel syntheses of diverse compound libraries. The synthesis of **6** is depicted in Scheme 1.

The conventional methods for the synthesis of the key starting materials, thiophene *o*-amino esters **7** require 3–4 h using variants of the Gewald reaction.[9–11] The use of microwave irradiation[7] offers an efficient method for the synthesis of 2-amino-3-carboethoxythiophenes **7** variously substituted at C-5 and C-6, in better yields (Scheme 1) and with a substantial reduction in the reaction time, compared to the conventional methods.[9–11]

* Corresponding author. Tel.: +91 9422322070; fax: +91 20 24354720.
E-mail address: ks_jain@vsnl.net (K. S. Jain).

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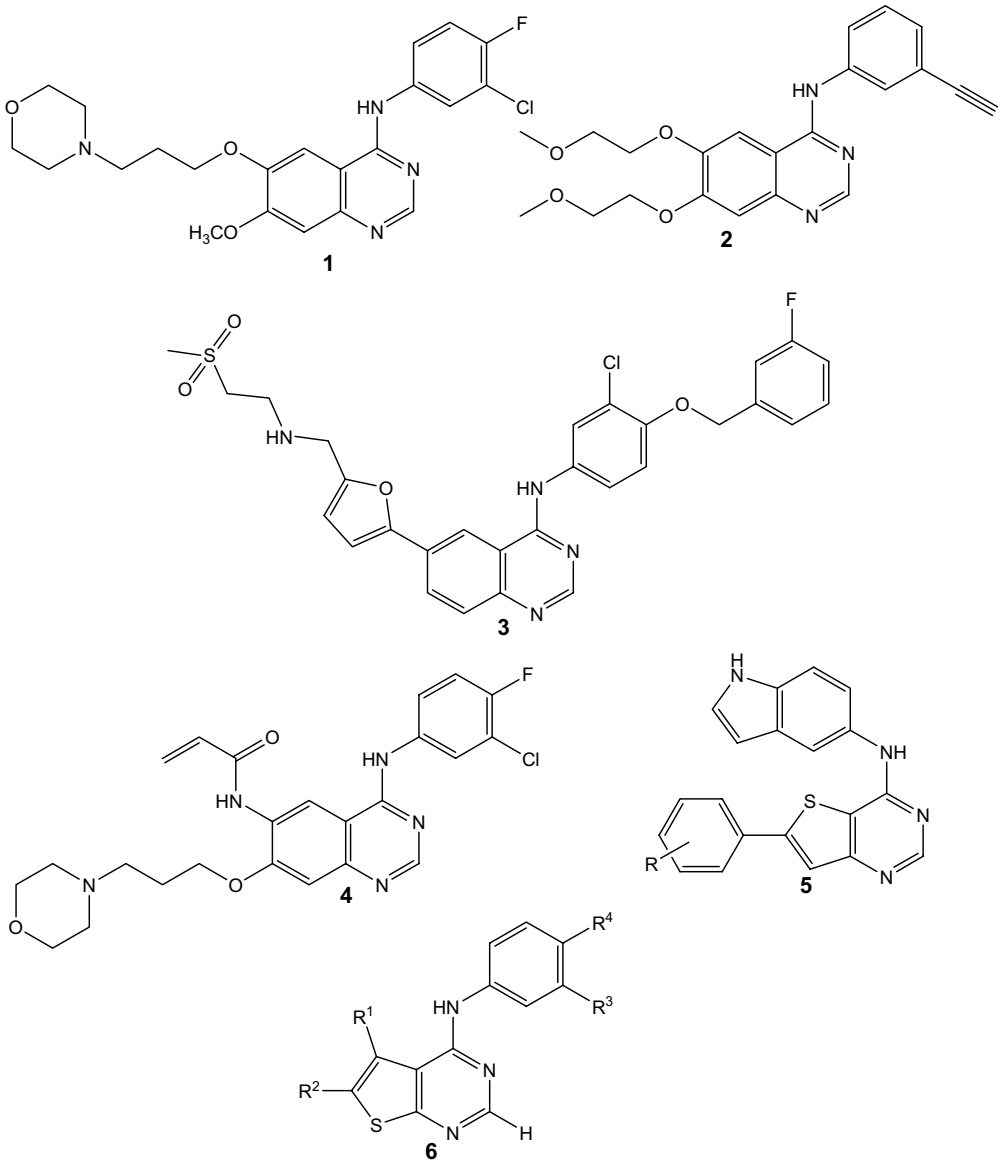


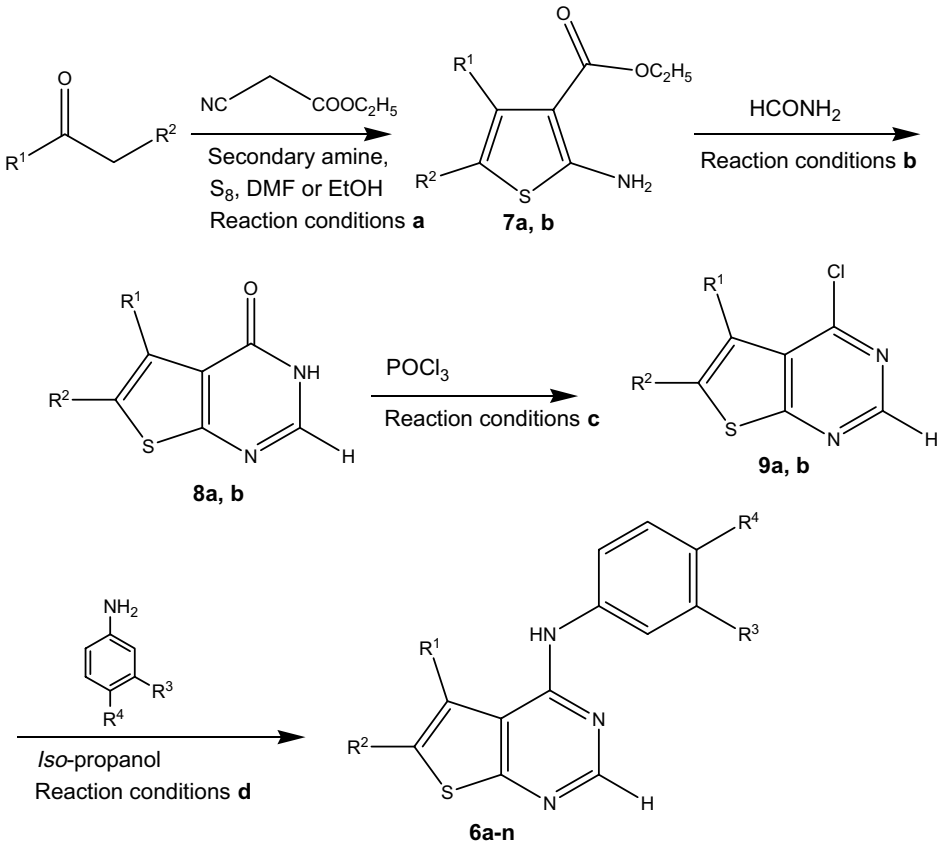
Fig. 1. Structures of some tyrosine kinase inhibitors.

For the conventional preparation of 2-unsubstituted-5,6-disubstituted-thieno[2,3-*d*]pyrimidin-4(3*H*)-ones **8**, the thiophene *o*-amino esters are cyclized with the 'C–N' component formamide at reflux for 8–12 h.

This same reaction under microwave irradiation at 350 W was accomplished in just 25–28 min to yield **8** in excellent yields, as well as, purities. The best result was obtained for compound **8a**, (87%), in which the reaction time was reduced from 8–10 h to 25 min.

The next step involved the chlorination of intermediates **8**. This is normally achieved using dimethylformamide and phosphorus oxychloride ($POCl_3$) or by the direct use of $POCl_3$ at reflux. In contrast, when compounds **8a**,**b** were treated with $POCl_3$ under MWI (350 W) for 10–12 min, the reaction went to completion. This microwave irradiation method for the chlorination not only reduced the overall reaction time from 12–14 h to 10–12 min, but also improved the purity and yields of the product. The physical data of **8a**,**b** and **9a**,**b** are shown in Table 1.

The final step in the synthesis of compounds **6** involved nucleophilic displacements of the 4-chloride atom of **9a**,**b** with a variety of substituted anilines. Using the conventional methodology this was achieved by treating 1 mol equiv of the appropriate 4-chloro compound **9** with two mol equivalents of the requisite aniline in *iso*-propanol at reflux for 5–9 h. In contrast, irradiating (350 W) the reaction mixture for 15–26 min yielded the target compounds **6a**–**n** in excellent yields. The addition of a catalytic quantity of concd HCl expedited the reaction. Such a synthesis



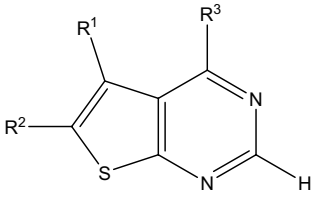
Scheme 1. Reaction conditions: (a) under microwave irradiation, 350 W, 2–5 min, (60–90%); (b) 350 W, 25–28 min, (87–92%); (c) 350 W, 10–12 min, (81–84%); (d) 350 W, 15–26 min, (68–98%).

completely under microwave irradiation was hitherto, unreported for these condensed thienopyrimidines (Table 2). The conventional reaction protocol requires long overall reaction times, often exceeding 24 h for the synthesis of these target compounds, thus, representing a serious detriment to adapting the conventional process for the parallel library synthesis of these compounds. In contrast, microwave irradiation greatly reduced the reaction times from hours to minutes and the overall four-step synthesis required a maximum of 2 h reaction time (not considering the time required for work-up as well as recrystallizations). Hence, the synthetic methodology reported herein is a very efficient method for the parallel library synthesis of condensed pyrimidines.

2. Experimental

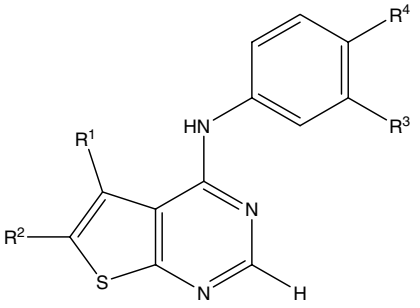
Microwave synthesizer, (Questron Technologies Corporation, Canada) QPro-M model monomode open-vessel was used for the synthesis.

Table 1
Physical data of 2-unsubstituted-5,6-disubstituted[2,3-*d*]pyrimidin-4(3*H*)-ones (**8a**,**b**) and 2-unsubstituted-4-chlorothieno[2,3-*d*]pyrimidines (**9a**,**b**)[12]



S. No.	R^1	R^2	R^3	Conventional method			Microwave-assisted method		
				Yield (%)	Mp (°C)	Time (h)	Yield (%)	Mp (°C) (solv. of crystn.)	Time (min)
8a	–$(CH_2)_4$–		OH	67	208–210	8–10	87	209–211 (DMF–MeOH)	25
8b	H	C_2H_5	OH	82	195–197	8–10	92	195–197 (DMF–MeOH)	28
9a	–$(CH_2)_4$–		Cl	75	114–115	12–14	84	113–115 (*n*-hexane)	12
9b	H	C_2H_5	Cl	71	53–56	12–14	81	54–56 (*n*-hexane)	10

Table 2
Physical data of 2-unsubstituted-4-arylaminothieno[2,3-*d*]pyrimidines (**6a**–**n**)[12]



S. No.	R^1	R^2	R^3	R^4	Conventional method			Microwave-assisted method		
					Yield (%)	Mp (°C)	Time (h)	Yield (%)	Mp (°C)[a] (solv. of crystn.)[b]	Time (min)
6a	–(CH_2)$_4$–		H	H	59	176–178	8–9	79	175–177 (I)	25
6b	–(CH_2)$_4$–		H	Br	84	158–160	8–9	97	158–160 (I)	23
6c	–(CH_2)$_4$–		H	Cl	73	136–138	8–9	82	134–137 (I)	22
6d	–(CH_2)$_4$–		H	F	81	166–168	8–9	87	167–169 (I)	20
6e	–(CH_2)$_4$–		Cl	F	62	135–137	8–9	75	136–138 (I)	20
6f	–(CH_2)$_4$–		H	OCH_3	69	145–147	8–9	78	144–146 (I)	22
6g	–(CH_2)$_4$–		H	CH_3	87	141–143	6–8	95	140–142 (I)	25
6h	H	C_2H_5	H	H	59	206–208	5–6	68	205–207 (B–M)	21
6i	H	C_2H_5	H	Br	86	234–237	5–6	96	234–236 (M–C)	19
6j	H	C_2H_5	H	Cl	65	138–140	5–6	78	139–141 (B–M)	16
6k	H	C_2H_5	H	F	61	220–222	5–6	77	220–222 (I–C)	18
6l	H	C_2H_5	Cl	F	70	170–172	5–6	91	171–173 (M–C)	15
6m	H	C_2H_5	H	OCH_3	82	139–141	5–6	92	138–140 (I)	20
6n	H	C_2H_5	H	CH_3	85	145–147	5–6	98	145–147 (B–C)	26

[a] The newly synthesized compounds were characterized by spectroscopic data[12] and by microanalysis (0.4% ± of calculated C and H).
[b] I = *iso*-propanol, B = benzene, C = chloroform, M = methanol.

3. General procedures

3.1. Reaction of 2-amino-3-carbethoxythiophenes (**7a**,**b**) *with formamide*

A mixture of 2-amino-3-carbethoxythiophene (**7**; 0.02 mol) and formamide (15 ml) was irradiated at 350 W for 25–28 min in a microwave synthesizer. The reaction mixture was allowed to cool to room temperature, and then poured on to ice water. The resulting precipitated solid was filtered, washed with chilled water and dried. The crude product on recrystallization from methanol–dimethylformamide (10:1) yielded the requisite thieno[2,3-*d*]pyrimidin-4(3*H*)-ones (**8a**,**b**).

3.2. Chlorination of thieno[2,3-d]pyrimidin-4(3H)-ones (**8a**,**b**) *to 4-chlorothieno[2,3-d]pyrimidines* (**9a**,**b**)

A mixture of the appropriate thieno[2,3-*d*]pyrimidin-4(3*H*)-one (**8a**,**b**; 0.02 mol) and phosphorus oxychloride (15 ml) was irradiated with microwaves (350 W) for 10–12 min. The extent of reaction was monitored by TLC. Thereafter, $POCl_3$ was removed under vacuum and the residue obtained was poured onto ice-cold water and neutralized with sodium bicarbonate. Recrystallization from *n*-hexane yielded crystalline 4-chloro-thieno[2,3-*d*]-pyrimidines (**9a**,**b**).

3.3. Reaction of 4-chlorothieno[2,3-d]pyrimidines (**9a**,**b**) *with various anilines to afford target compounds* (**6a**–**n**)

A mixture of the appropriate 4-chlorothieno[2,3-*d*]-pyrimidine (**9a**,**b**; 0.022 mol) and the aniline (0.044 mol) in *iso*-propanol (20 ml) was irradiated with microwaves at 350 W for 15–26 min. The reaction mixture was chilled overnight at 5 °C and the separated solid was filtered, washed with cold *iso*-propanol and air-dried. The crude product, then on recrystallization from *iso*- propanol, afforded 4-arylaminothieno[2,3-*d*]pyrimidines (**6a**–**n**).

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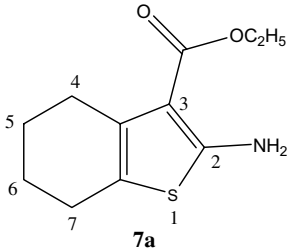
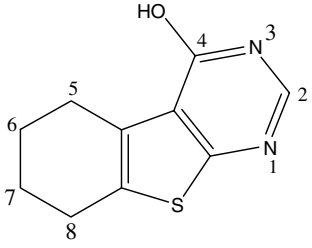
12. Analytical data for the representative compounds

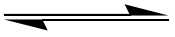


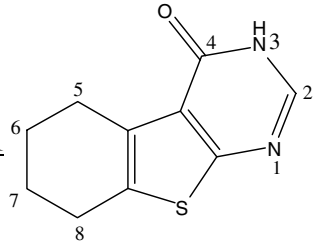
7a

Compound **7a**: IR KBr, cm^{-1}: 3415 and 3305 (ν_{NH_2}), 2916 (ν_{CH_2}), 1651 (ν_{CO}); ^1H NMR (300 MHz, $CDCl_3$): δ 1.33 (3H, t, $J = 6.9$ Hz, $COOCH_2CH_3$), 1.75 (4H, d, $J = 6.0$ Hz, CH_2 at 5 and 6), 2.51 (2H, s, CH_2 at 4), 2.68 (2H, s, CH_2 at 7), 4.25 (2H, q, $J = 7.2$, $COOCH_2CH_3$), 5.87 (2H, br s, NH_2); MS *m/z* 225 (M^+); Anal. Calcd for $C_{11}H_{15}NO_2S$: C, 58.64; H, 6.71. Found: C, 58.44; H, 6.61.



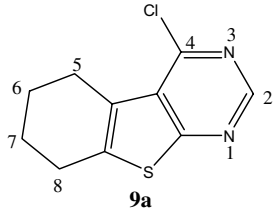
8a i





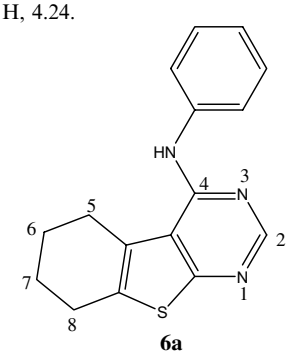
8a ii

Compound **8a**: IR KBr, cm^{-1}: 2938 (ν_{CH_2}), 1658 (ν_{CO}); ^1H NMR (300 MHz, $CDCl_3$): δ 1.86 (4H, d, $J = 6$ Hz, CH_2 at 6 and 7), 2.86 (2H, s, CH_2 at 5), 3.02 (2H, s, CH_2 at 8), 7.24 (1H, s, CH at 2), 8.07 (1H, br d, $J = 6.0$ Hz, NH at 3); MS *m/z* 206 (M^+); Anal. Calcd for $C_{10}H_{10}N_2OS$: C, 58.23; H, 4.89. Found: C, 58.27; H, 4.69.



9a

Compound **9a**: IR KBr, cm^{-1}: 2934 (ν_{CH_2}), 730 (ν_{C-Cl}); ^1H NMR (300 MHz, $CDCl_3$): δ 1.91 (4H, d, $J = 3.0$ Hz, CH_2 at 6 and 7), 2.86 (2H, s, CH_2 at 5), 3.09 (2H, s, CH_2 at 8), 8.69 (1H, s, CH at 2); MS *m/z* 226 (M^{+2}); Anal. Calcd for $C_{10}H_9ClN_2S$: C, 53.45; H, 4.04. Found: C, 53.55; H, 4.24.



6a

Compound **6a**: IR KBr, cm^{-1}: 3428 (ν_{NH}), 2925 (ν_{CH_2}), 1602 (ν_{NH}); ^1H NMR (300 MHz, $CDCl_3$): δ 1.90 (4H, d, $J = 9$, CH_2 at 6 and 7), 2.82 (2H, s, CH_2 at 5), 3.03 (2H, s, CH_2 at 8), 7.08–7.37 (3H, m, Ar-H), 7.24 (1H, s, NH at 4), 7.61 (2H, d, $J = 9.0$ Hz, Ar-H), 8.41 (1H, s, CH at 2); MS *m/z* 281 (M^+); Anal. Calcd for $C_{16}H_{15}N_3S$: C, 68.30; H, 5.37. Found: C, 68.39; H, 5.30.