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Research Article

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Synthesis of thieno[2,3-d]pyrimidine analogues from a thiophene moiety

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Abstract

Four novel thieno[2,3-d]pyrimidine analogues, **6a-b** and **7a-b** were synthesized by using 6-Bromo-2-chloro-thieno[2,3-d]pyrimidine (**3**), which was synthesized from commercially available thiophene derivative, 2-aminothiophene-3-carboxylate (**1**). Initially, pyrimidine framework was performed by strong heating of **1** in formamide and then by using Vilsmeier reagent, conversion of 4-oxo group of **2** into chlorine was achieved. By regioselectivity approach at position 6 of **3** with *n*-BuLi and CBr_4 at low temperature gives **4a-b**. Introduction of Suzuki coupling reactions on **4a-b** with 4-fluorophenylboronic acid afforded the desired compounds **5a-b** respectively. Finally, by using different reagents under mild and vigorous conditions, the position 4 of **5a-b, 6a-b** and **7a-b** were synthesized.

Key words: Thieno[2,3-d]pyrimidine, 6-Bromo-2-chloro-thieno[2,3-d]pyrimidine, Vilsmeier reagent and Suzuki coupling.

1. Introduction

Thienopyrimidines are a class of fused heterocycles which are commonly used for synthesis of new potential therapeutic drugs (Hala *et al.*, 2011). There are three isomeric thienopyrimidines corresponding to the three possible types of annulation of thiophene to the pyrimidine ring: thieno[2,3-d]pyrimidine, thieno[3,4-d]pyrimidine, and thieno[3,2-d]pyrimidine. The similarity between the physicochemical properties of benzene and thiophene is striking (Stewart *et al.*, 2001). For example, the boiling point of benzene is 81.1°C and the one of thiophene is 84.4°C (at 760mm Hg). So, thiophene and benzene are a well-known example of bioisosterism (Cannito *et al.*, 1990). The change of a benzene moiety into a thiophene often results in superior pharmacodynamic, pharmacokinetic, or toxicological properties (Santagati *et al.*, 1994). For example, the thiophene analogue of piroxicam (a non-steroid anti-inflammatory agent used in arthritis patients) has the same biological activity, with the same mechanism of action as piroxicam, and even displayed a longer plasma half-life than piroxicam (Binder *et al.*, 1987). Thiophene isosteres of mianserin (a tetracyclic antidepressive agent) also act as serotonin receptor (5-HT) antagonists (Ives and Heym, 1989) In addition, thienopyrimidine derivatives have Antiallergic (Gillespie *et al.*, 1985), antiatherosclerotic (Gomoll and Temple, 1987), antibacterial (Bousquet *et al.*, 1985), antidepressive (El-Kashef *et al.*, 1993), antidiabetic, antihypertensive (Russell *et al.*, 1988), antihistaminic (Shishoo *et al.*, 2000), analgesic and anti-inflammatory (Devani *et al.*, 1976; Russo *et al.*, 1989; Shwarsinh *et al.*, 2000; Perrissian *et al.*, 1988) antiviral (Kent S. Gates and Richard B. Silverman, 1990) and spasmolytic activities (Oganisyan *et al.*, 2007). The exchange of a phenyl ring by a thiophene ring in bicyclic derivatives can generate three regioisomers. For example, Blair and coworkers described the replacement of the phenyl ring of *N*,*N*-dimethyltryptamine by a thiophene moiety, giving rise to three isomers: thieno[3,2-b]pyrrole, thieno[2,3-b]pyrrole and thieno[3,4-b]pyrrole. Biological evaluation demonstrated that both thieno[3,2-b]pyrrole and thieno[2,3-b]pyrrole showed similar activity as the parent indole-

- analogue, whereas thieno[3,4-b]pyrrole lost activity. As a logical consequence of thiophene–phenyl isosterism, thienopyrimidines can be considered as bioisosteres of quinazolines, which are extensively described in scientific and patent literature as displaying a plethora of biological activities. The synthesis of thienopyrimidine derivatives as potential surrogates for the quinazoline core structure has therefore become a routine strategy in modern drug design and development (Kharizomenova *et al.*, 1981).

Synthetic approaches towards thieno-pyrimidines can be divided into two main groups according to the type of starting material. Either, the synthesis starts from a pyrimidine derivative and a thiophene ring is then constructed, or a thiophene analogue is used as starting material, followed by the formation of a pyrimidine ring. Keeping this in view, as there are no systematic studies done on how to elaborate the chemistry of thieno[2,3-d]pyrimidines compounds in a systematic way. We planned to synthesis thieno[2,3-d]pyrimidines by using some efficient methods, new intermediates and reagents.

2. Material and Methods

2.1 Chemicals and Instrumentation

General solvents were dried over standard drying agents and freshly distilled prior to use. The reagents were purchased from Aldrich and Acros and were used without further purification unless otherwise stated. All moisture-sensitive reactions were carried out under N_2. Organic solutions were dried (Na_2SO4) and concentrated in vacuum below 408. Column chromatographic (CC): silica gel (SiO_2, 60–120 mesh; Acme's). Optical rotations: HoribaSEPA-300 high-sensitive polarimeter; at 258. IR Spectra: Perkin-Elmer-IR-683 spectrophotometer with NaCl optics; n˜ in cm^{-1}. ^{1}H-(300MHz) and ^{13}C-NMR (75MHz) Spectra: Bruker-Avance-300 instrument; in $CDCl_3$; d in ppm rel. to Me_4Si as internal standard, *J* in Hz. MS: Agilent Technologies 1100 series (Agilent Chemistation Software); in m/z.

2.2 Method for development of analogues and their chemistry

6-Bromo-2-chloro-thieno[2,3-d]pyrimidine **3** was synthesized from commercially available methyl 2-aminothiophene-3-carboxylate **1** by a strong reflux (Fig 1). In order to construct the pyrimidine scaffold, compound **1** was heated in formamide. Conversion of the 4-oxo group into chlorine was achieved in a good yield with oxalyl chloride and DMF (Vilsmeier reagent). Regioselective introduction of a bromine at position 6 was performed with *n*-BuLi and carbon tetrabromide as bromine source at low temperature (-78^{o}C). Two major products **4a** and **4b** were isolated in a ratio of 1:1, after purification by flash chromatography. From the mass spectral and ^{1}H-NMR data of compound **4b**, it is clear that a butyl group is present on the thienopyrimidine scaffold. Heteronuclear Multiple Bond Correlation (HMBC) spectroscopy was used to determine the exact regiochemistry.

A direct coupling (1*J*) of the aromatic proton (Ha: δ = 7.4 ppm) and a ^{13}C signal at 122 ppm was detected. The carbon signal of C(2) is usually seen above 150 ppm, whereas the carbon at position 5 is observed around 120 ppm, indicating that the aromatic proton is present at position 5. Only one HMBC correlation (2*J*) between the methylene protons (Hb) of *n*-butyl substituent and a carbon (at δ = 150 ppm) is observed, which supports the fact that the *n*-butyl group is attached to C(2). If C(5) would bear the butyl group, three HMBC cross-peaks should be observed: one 2*J* between C(5) and Hb and two 3*J* between Hb and C(4a) and C(6). If the butyl group would have been present at position 6, there should be two possible HMBC correlations: one 2*J* between C(6) and Hb, and one 3*J* between Hb and C(5). In addition, no correlation was detected between the aromatic proton (Ha) and the methylene carbon of *n*-butyl group, which means that the aromatic proton and butyl group are not placed next to each other. These NMR data also confirm that bromination takes place at position 6 of the thieno[2,3-d]pyrimidine scaffold. Standard reaction conditions for Suzuki coupling of compounds **4a** and **4b** with 4-fluorophenylboronic acid afforded the desired compounds **5a** and **5b** respectively. The remaining

chlorine atom was displaced by and 2-(4-chlorophenoxy)-1-(piperazin-1-yl)ethanone under mild conditions yielding compounds and **7a** and **7b.** For the introduction of anilino moiety at position 4, more vigorous conditions were needed due to the poor nucleophilicity of the aniline nitrogen, 3-chloro-4-fluoroaniline was used to displace chlorine atom which yields **6a** and **6b**.

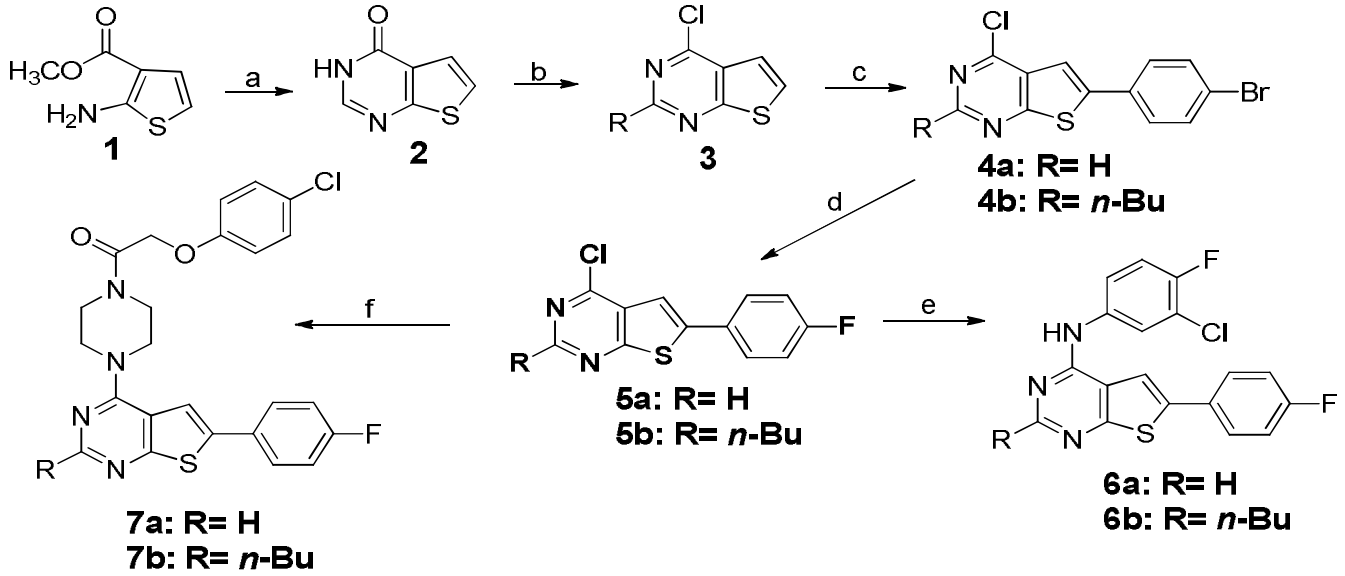

Fig 1. a) formamide, reflux, 3h; b) oxalyl hloride, DMR, CH_2Cl_2, 0°C to reflux, 2.5h; c) *n*-BuLi, CBr_4, THF, -78°C 20min, then rt for 2h; d) 4-fluorophenylboronic acid, $Pd(PPh_3)_4$, K_2CO_3, dioxane/water (3:1 v/v), reflux, 3h; e) 3-chloro-4-fluoroaniline, diclhloro/ethane/*t*-BuOH (1:1 v/v), reflux, 14h; f) 2-(4-Chlorophenoxy)-1-(piperazin-1-yl)ethanone, dioxane, Net_3, 70°C, 24h.

3. Results and Discussion

Procedure for Preparation of Thieno[2,3-d]pyrimidin-4(3*H*)-one **(2).** A solution of methyl 2-aminothiophene-3-carboxylate **1** (3g, 19.1mmoL) in formamide (95mL) was heated at 190°C for 4h. The cooled mixture was poured into water. The precipitate was filtered off, washed with water and dried. The crude product was purified by silica gel chromatography (CH_2Cl_2/MeOH 50:1) to yield the title compound as a white solid **[Fig 1-(1) to (2)]** (1.93g, 66%). mp=265°C. ^{1}H NMR (300MHz, DMSO, 25°C): δ = 12.49 (s, 1H, NH), 8.13 (s, 1H, CH), 7.58 (d, *J* = 5.8Hz, 1H, CH), 7.39 (d, *J* = 5.8Hz, 1H, CH) ppm. ^{13}C NMR (75MHz, DMSO, 25°C): 164.2, 157.5, 145.6, 124.6, 123.8, 121.6 ppm. HRMS: calcd for $C_6H_5N_2OS$ $[M+H]^+$ 153.01226, found 153.01155.

4-Chlorothieno[2,3-d]pyrimidine **(3).** DMF (1.53mL, 19.7mmoL) in dichloromethane (50mL) was cooled to 0°C and oxalyl chloride (2.5mL, 29.6mmoL) was added slowly forming a white gel. Thieno[2,3-d]pyrimidin-4(3*H*)-one **2** (1.5g, 9.86mmoL) was added and the reaction mixture was refluxed for 3h. The mixture was cooled down to room temperature and poured into water. The mixture was extracted with dichloromethane, dried over sodium sulfate and concentrated *in vacuo*. The crude residue was purified by silica gel chromatography (EtOAc/hexane 15:1) to yield the title compound as a white solid **[Fig 1-(2) to (3)]** (1.61g, 96%). mp=105°C. ^{1}H NMR (300MHz, $CDCl_3$, 25°C): δ = 8.88 (s, 1H, CH), 7.64 (d, *J* = 6.0Hz, 1H, CH), 7.47 (d, *J* = 5.8Hz, 1H, CH) ppm. ^{13}C NMR (75MHz, $CDCl_3$, 25°C): 168.8, 155.0, 152.7, 129.5, 128.5, 119.9 ppm. HRMS: calcd for $C_6H_4ClN_2S$ $[M+H]^+$ 170.97837, found 170.97804.

6-Bromo-4-chlorothieno[2,3-d]pyrimidine **(4a)** and 6-bromo-2-butyl-4-chlorothieno[2,3-d]pyrimidine **(4b)**. *n*-BuLi (1.6M in hexane, 1.9mL, 2.5mmoL) in THF (8mL) was cooled to -78°C. 4-chlorothieno[2,3-d]pyrimidine **3** (0.34g, 2mmoL) was dissolved in THF (2mL) and slowly added to the reaction mixture over 5min. After 20min, CBr_4 (0.73g, 2.2mmoL) in THF (3mL) was slowly added to the reaction mixture. The temperature was

maintained at -78°C for 20min then warmed to room temperature for 2h. The mixture was poured into water and extracted with chloroform, dried over sodium sulfate, and concentrated *in vacuo*. The crude residue was purified by silica gel chromatography (EtOAc/hexane 40:1) to yield two pure compounds a white solid (compound **4a**: 0.13g, 25% and compound **4b**: 0.16g, 26%).

Compound **4a [Fig 1-(3) to (4a)]**: ^{1}H NMR (300MHz, $CDCl_3$, 25°C): δ = 8.82 (s, 1H, H-2), 7.49 (s, 1H, H-5) ppm. ^{13}C NMR (75MHz, $CDCl_3$, 25°C): 169.7, 153.1, 143.8, 130.8, 122.5, 119.0 ppm.

Compound **4b [Fig 1-(3) to (4b)]**: ^{1}H NMR (300MHz, $CDCl_3$, 25°C): δ = 7.4 (s, 1H, H-5), 2.99 (t, *J*= 7.5Hz, 2H, $CH_2CH_2CH_2CH_3$), 1.83 (quint, *J*= 7.6Hz, 2H, $CH_2CH_2CH_2CH_3$), 1.42 (sixtet, *J*= 7.4Hz, 2H, $CH_2CH_2CH_2CH_3$), 0.96(t, *J*= 7.4Hz, 2H, $CH_2CH_2CH_2CH_3$) ppm. ^{13}C NMR (75MHz, $CDCl_3$, 25°C): 167.3, 153.0, 140.5, 127.9, 122.2, 117.1, 38.9, 30.9, 22.6, 14.0 ppm.

4-Chloro-6-(4-fluorophenyl)thieno[2,3-d] pyrimidine **(5a)**. A solution of 6-bromo-4-chlorothieno [2, 3-d] pyrimidine **4a** (0.12g, 0.48mmoL), 4-fluorophenylboronic acid (67mg, 0.48mmoL), K_2CO_3 (0.266g, 1.92mmoL) and $Pd(PPh_3)_4$ in dioxane/H_2O (3:1, 3mL) was refluxed under N_2 for 2h. After cooling to room temperature, 1N HCl was added slowly to neutralize the mixture to pH=7-8. The mixture was extracted with CH_2Cl_2, washed with water and brine and dried over Na_2SO_4. After removing the solvents under reduced pressure, the crude residue was purified by silica gel chromatography (hexane/EtOAc 30:1) to yield the title compound as a pale yellow solid **[Fig 1-(4a) to (5a)]** (60mg, 47%). mp= 144°C. ^{1}H NMR (300MHz, $CDCl_3$, 25°C): δ = 8.82 (s, 1H, CH-2), 7.70-7.74 (m, 2H, PhH), 7.52 (s, 1H, CH-5), 7.19 (t, *J*= 8.4Hz, 2H, PhH) ppm. ^{13}C NMR (75MHz, $CDCl_3$, 25°C): 168.5, 168.3 (d, *J*= 249.8Hz), 153.6, 152.8, 145.3, 131.4 (d, *J*= 5.8Hz), 129.0 (d, *J*= 8.3Hz), 123.3, 116.7 (d, *J*= 22.0Hz), 114.5 ppm. HRMS: calcd for $C_{12}H_7ClFN_2S$ $[M+H]^+$ 265.00025, found 264.99949.

2-Butyl-4-chloro-6-(4-fluorophenyl)thieno [2,3-d]pyrimidine **(5b)**. This compound was prepared from **4b** in a yield of 57%, according to the procedure for the synthesis of compound **5a [Fig 1-(4b) to (5b)]**. ^{1}H NMR (300MHz, $CDCl_3$, 25°C): δ = 7.57-7.62 (m, 2H, PhH), 7.36 (s, 1H, H-5), 7.08 (t, *J*= 8.4Hz, 2H, PhH), 2.94 (t, *J*= 7.6Hz, 2H, $CH_2CH_2CH_2CH_3$), 1.78 (quint, *J*= 7.6Hz, 2H, $CH_2CH_2CH_2CH_3$) , 1.36 (sixtet, *J*= 7.5Hz, 2H, $CH_2CH_2CH_2CH_3$) , 0.89 (t, *J*= 7.4Hz, 2H, $CH_2CH_2CH_2CH_3$) ppm. ^{13}C NMR (75MHz, $CDCl_3$, 25°C):169.0, 166.9, 163.6 (d, *J*= 249.2Hz), 154.0, 143.6, 129.2 (d, *J*= 3.3Hz), 128.7 (d, *J*= 8.3Hz), 123.2, 116.5 (d, *J*= 21.9Hz), 114.4, 39.1, 31.1, 22.7, 14.1 ppm. HRMS: calcd for $C_{16}H_{15}ClFN_2S$ $[M+H]^+$ 321.06285, found 321.06206.

N-(3-Chloro-4-fluorophenyl)-6-(4-fluorophen-yl) thieno [2,3-d]pyrimidin-4-amine **(6a)**. To a solution of 4-chloro-6-(4-fluoro-phenyl)thieno[2,3-d]pyrimidine **5a** (40mg, 0.15mmoL) in 1,2-dichloroethane/*t*-BuOH (1:1, 1mL) was added 3-chloro-4-fluoroaniline (22mg, 0.15 mmoL). The mixture was heated at 90°C for 48h. After cooling down to room temperature, the solvents were removed under reduced pressure. The crude residue was purified by silica gel chromatography (CH_2Cl_2/MeOH 100:1) to yield the title compound as a white solid **[Fig 1-(5a) to (6a)]** (28mg, 50%). mp=238-239°C. ^{1}H NMR (300MHz, $CDCl_3$, 25°C): δ = 8.61 (s, 1H, H-2), 7.89 (dd, *J*= 6.5Hz, *J*= 2.6Hz, 1H, PhH), 7.62-7.67 (m, 2H, PhH), 7.48-7.53 (m, 1H, PhH), 7.28 (s, 1H, H-5), 7.13-7.26 (m, 3H, PhH), 6.87 (s, 1H, NH) ppm. ^{13}C NMR (75MHz, $CDCl_3$, 25°C): 167.3, 163.4 (d, *J*= 248.5Hz), 155.2 (d, *J*= 245.3Hz), 154.2, 153.2, 141.6, 134.9 (d, *J*= 3.3Hz), 129.6, 128.5 (d, *J*= 8.2Hz), 124.1, 121.6 (d, *J*= 6.8Hz), 121.5 (d, *J*= 19.2Hz), 118.3, 117.0 (d, J= 21.9Hz), 116.5 (d, J= 21.9Hz), 111.8 ppm. HRMS: calcd for $C_{18}H_{11}ClF_2N_3S$ $[M+H]^+$ 374.03303, found 374.03216.

2-Butyl-*N*-(3-chloro-4-fluorophenyl)-6-(4-fluor-ophenyl)thieno[2,3-d]pyrimidin-4-amine **(6b)**. This compound was prepared from **5b** in a yield of 47%, according to the procedure for the synthesis of compound **4.8a [Fig 1-(5b) to (6b)]**. mp 157°C ^{1}H NMR (300MHz, $CDCl_3$, 25°C): δ = 8.03 (dd, *J*= 6.30Hz, *J*= 2.3Hz, 1H, PhH), 7.59-7.64 (m, 2H,

PhH), 7.48-7.53 (m, 1H, PhH), 7.23 (s, 1H, H-5), 7.10-7.19 (m, 3H, PhH, PhH), 6.89 (s, 1H, NH), 2.93 (t, *J*= 7.5Hz, 2H, $CH_2CH_2CH_2CH_3$), 1.87 (quint, *J*= 7.6Hz, 2H, $CH_2CH_2CH_2CH_3$), 1.45 (sixtet, *J*= 7.5Hz, 2H, $CH_2CH_2CH_2CH_3$) , 0.98 (t, *J*= 7.3Hz, 2H, $CH_2CH_2CH_2CH_3$) ppm. ^{13}C NMR (75MHz, $CDCl_3$, 25^{o}C): 168.1, 166.8, 163.2 (d, *J*= 247.9Hz), 154.7 (d, *J*= 244.4Hz), 154.1, 140.0, 135.6 (d, *J*= 3.2Hz), 129.9 (d, *J*= 3.3Hz), 123.8 (d, *J*= 8.3Hz), 123.3, 121.2 (d, *J*= 18.6Hz), 120.5 (d, *J*= 6.7Hz), 116.7 (d, *J*= 22.0Hz), 116.4 (d, *J*= 21.8Hz), 115.9, 111.8, 39.3, 30.8, 22.7, 14.2 ppm. HRMS: calcd for $C_{22}H_{19}ClF_2N_3S$ $[M+H]^+$ 430.0956, found 430.0959

2-(4-Chlorophenoxy)-1-(4-(6-(4-fluorop-henyl) thieno[2,3-d] pyrimidin-4-yl) piperazin-1-yl) ethanone **(7a)**. To a solution of 4-chloro-6-(4-fluorophenyl)thieno[2,3-d]pyrimidine **5a** (20mg, 0.08mmoL) and triethylamine (42µL, 0.3mmoL) in dioxane (1mL) was added 2-(4-chlorophenoxy)-1-(piperazin-1-yl)ethanone (25mg, 0.1mmoL). The mixture was heated at 60^{o}C for 2h. After cooling down to room temperature, the solvents were removed under reduced pressure. The crude residue was purified by silica gel chromatography (CH_2Cl_2/MeOH 50:1) to yield the title compound as a white solid **[Fig 1-(7a) to (5a)]** (27mg, 75%). mp=112^{o}C. ^{1}H NMR (300MHz, $CDCl_3$, 25^{o}C): δ = 8.51 (s, 1H, CH-2), 7.60-7.65 (m, 2H, PhH), 7.36 (s, 1H, CH-5), 7.26 (d, *J*= 8.8Hz, PhH), 7.14 (t, *J*= 8.5Hz, 2H, PhH), 6.91 (d, *J*= 8.8Hz, 2H, PhH), 4.75 (s, 2H, CH2), 3.95 (br s, 4H, NCH_2), 3.82 (br s, 4H, NCH_2) ppm. ^{13}C NMR (75MHz, $CDCl_3$, 25^{o}C): 169.3, 166.8, 163.3 (d, *J*= 248.2Hz), 158.5, 156.5, 152.9, 139.5, 129.8, 128.4 (d, *J*= 8.2Hz), 127.1, 116.4 (d, *J*= 21.9Hz), 116.1, 115.2, 68.8, 47.2, 46.8, 45.1, 42.0 ppm. HRMS: calcd for $C_{24}H_{21}ClFN_4O_2S$ $[M+H]^+$ 483.10578, found 483.10438.

1-(4-(2-Butyl-6-(4-fluorophenyl) thieno [2,3-d] pyrimidin-4-yl) piperazin-1-yl)-2-(4-Chlorophen- oxy) ethanone **(7b).** This compound was prepared from **5b** in a yield of 57%, according to the procedure for the synthesis of compound **7a [Fig 1-(5b) to (7b)]**. mp=126^{o}C. ^{1}H NMR (300MHz, $CDCl_3$, 25^{o}C): δ = 7.58-7.63 (m, 2H, PhH), 7.32 (s, 1H, CH-5), 7.26 (d, *J*= 9.0Hz, PhH), 7.13 (t, *J*= 8.6Hz, 2H, PhH), 6.91 (d, *J*= 9.0Hz, 2H, PhH), 4.74 (s, 2H, CH_2), 3.95 (br s, 4H, $N(CH_2)_2$), 3.81 (br s, 4H, $CON(CH_2)_2$), 2.84 (t, *J*= 7.6Hz, 2H, $CH_2CH_2CH_2CH_3$), 1.80 (quint, *J*= 7.6Hz, 2H, $CH_2CH_2CH_2CH_3$), 1.42 (sixtet, *J*= 7.6Hz, 2H, $CH_2CH_2CH_2CH_3$) , 0.96 (t, *J*= 7.6Hz, 2H, $CH_2CH_2CH_2CH_3$) ppm. ^{13}C NMR (75MHz, $CDCl_3$, 25^{o}C):169.3, 166.8, 163.3 (d, *J*= 248.2Hz), 158.5, 156.5, 152.9, 139.5, 129.8, 128.4 (d, *J*= 8.2Hz), 127.1, 116.4 (d, *J*= 21.9Hz), 116.1, 115.2, 68.8, 47.2, 46.8, 45.1, 42.0 ppm. HRMS: calcd for C28H29ClFN4O2S $[M+H]^+$ 539.16838, found 539.16680.

Conclusion

A set of thieno[2,3-d]pyrimidine analogues was synthesized from suitable 2-aminothiophene-3-carboxylate building blocks, which is commercially available. The chemistry has been worked out in such a way that different substituents at position 4 and 6 can be introduced.

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Conflict of Interest

We have none to declare.

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