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MEDICINAL CHEMISTRY RESEARCH

ORIGINAL RESEARCH

Synthesis and antimicrobial evaluation of novel benzo[b]thiophenes comprising β-lactam nucleus

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Abstract Synthesis, structural characterization, and biological activity studies of benzo[*b*]thiophene derivatives containing β-lactam nucleus are described. Cycloaddition of azomethines (**4a–j**) to in situ-generated ketenes from 2,4-dichlorophenoxyacetic acid, in the presence of triethylamine and benzenesulfonyl chloride afforded the title compounds (**5a–j**). The stereochemical course of reaction depends on both the substituents on the ketenes as well as on the imines. The mechanism for the formation of *cis*/*trans* derivative is presented.

Keywords Benzo[*b*]thiophene · β-Lactam · 2-Azetidinone · Antimicrobial activity

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Introduction

Over the recent years, there has been an increasing interest in the chemistry of thiophenes because of their biological significance. Many of them have been widely investigated for several therapeutic uses (Wardakhan *et al*., 2005). The β-lactam heterocycles are still the most prescribed antibiotics used in medicine. They are considered as an important contribution of science to humanity (Southgate, 1994; Morin and Gorman, 1982). The most widely used antibiotics, such as the penicillins, cephalosporins, carumonam, aztreonam, thienamycine, and the nocardicins all contain β-lactam rings (Mata *et al*., 2003). The long-term use of β-lactam antibiotics exerts selective pressure on bacteria and permits the proliferation of resistant organisms (Page, 1992). A comparative study of current antibiotics with those from previous decades shows an alarming increase in bacterial resistance to β-lactam antibiotics (Niccolai *et al*., 1997; Chu *et al*., 1996). The development of several synthetic and semi-synthetic β-lactam antibiotics by the pharmaceutical industry was due to the growing resistance of bacteria toward the β-lactam antibiotics and the need for medicines with a more specific antibacterial activity (Van der Steen and Van Koten, 1991).

Keeping in mind the biomedical applications, as a continuation of our previous study (Desai and Shah, 2003), and with a view to further assess the pharmacological profile of this class of compounds, it was thought worthwhile to synthesize some new congeners of β-lactam heterocycles by incorporating the benzo[*b*]thiophene and β-lactam in a single molecular framework with a potential spectrum of bio-responses. The antimicrobial activities of the newly synthesized compounds against gram-positive and gram-negative bacteria were studied.

Results and discussion

Chemistry

Several methods are well known for the synthesis of benzo[*b*]thiophenes (Radl *et al*., 2000; Carrington *et al*., 1971; Beck, 1972; Beck and Yahner, 1974; Li *et al*., 1992). In this study, we have utilized Gewald reaction for the synthesis of benzo[*b*]thiophene derivative **3**. Synthesis of 2-(3-((*E*)-2-(5-chloro-3-methyl-1-phenyl-1*H*-pyrazol-4-yl)vinyl)-5,5-dimethylcyclohex-2-enylidene)malononitrile **2** was accomplished by condensing 2-(3,5,5-trimethylcyclohex-2-enylidene)malononitrile **1** with 5-chloro-3-methyl-1-phenyl-1*H*-pyrazole-4-carbaldehyde. This **2** on reaction with sulfur and morpholine furnished 2-amino-5-((*E*)-2-(5-chloro-3-methyl-1-phenyl-1*H*-pyrazol-4-yl)vinyl)-6,7-dihydro-7,7-dimethylbenzo[b]thiophene-3-carbonitrile **3**. A series of azomethines (**4a–j**) were prepared by condensing compound **3** with a variety of aromatic aldehydes. Cycloaddition of (**4a–j**) to 2,4-dichlorophenoxy acetic acid, in the presence of triethylamine and benzenesulfonyl chloride afforded the title compounds 2-(3-(2,4-dichlorophenoxy)-2-(aryl)-4-oxoazetidin-1-yl)-5-(2-(5-chloro-3-methyl-1-phenyl-1*H*-pyrazol-4-yl)vinyl)-6,7-dihydro-7,7-dimethylbenzo[b]thiophene-3-carbonitriles **(5a–j)** (Scheme 1; Fig. 1).

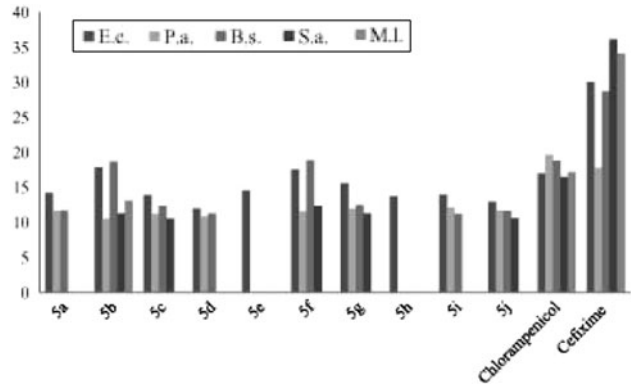
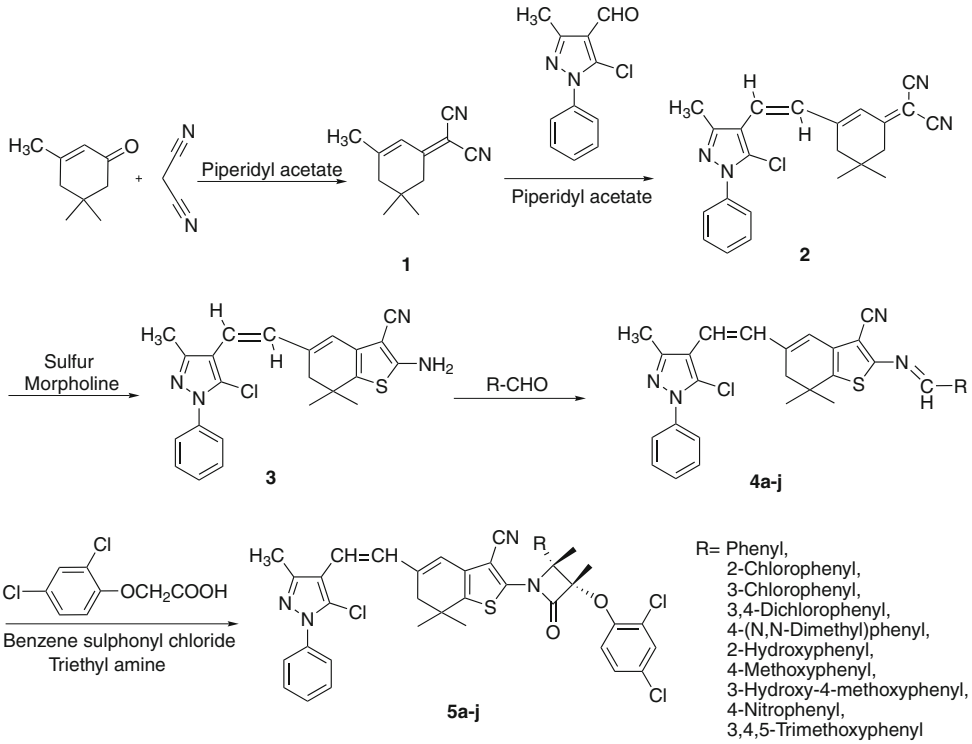


Fig. 1 Antibacterial activity of **5a–j**

Stereochemistry

The formation of *cis* or *trans* 2-azitidinone (*β*-lactam) takes place via (2 + 2) cycloaddition involving a ketene derived from 2,4-dichlorophenoxyacetic acid and azomethines (**4a–j**) obtained by the condensation of aminobenzo[*b*]thiophene derivative with various aromatic aldehydes. The *cis–trans* stereochemistry depends mainly upon the substituents on the ketene parts as the imine (azomethines) is usually presumed to exist in the more stable *E*-configuration. The stereochemical outcome can be explained involving the

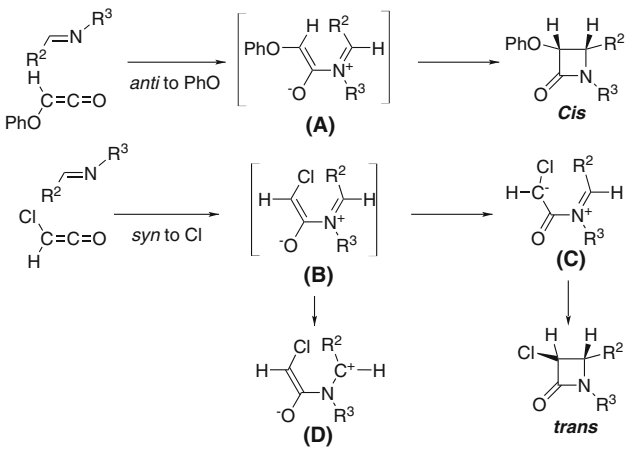
Scheme 1 Reaction scheme



diene intermediate through the concept of torquoselectivity advanced by Houk and coworkers (Rondan and Houk, 1985), and later utilized by Lopez et al. (Lopez *et al*., 1993). Based on this concept, the preference of donor (alkoxy, aryloxy) or acceptor (thioalkoxy, thioaryloxy, chloride) groups on the ketene would decide about the structure of the involved intermediate (**A**) or (**B**). The zwitterionic intermediate (**A**) forms a *cis* *β*-lactam with phenoxy (donor) group barring ketene, whereas such an intermediate, which is more stabilized in the resonance form (**B**) by sulfur (or any acceptor) on ketene and would be a major contributor to resonance hybrid, affords *trans* *β*-lactam. The structure of the diene intermediate would be (**A**) or (**B**) resulting from the addition of the imine *anti* or *syn* to the donor or acceptor groups of ketene. Consequently, conrotatory ring closure would then lead to the formation of *cis*-or *trans*-*β*-lactam. However, in the present case, the presence of donor aryloxy (phenoxy) group on the ketene leads to the formation of intermediate (**A**) and eventually in the formation of *cis* *β*-lactams (**5a–j**), which is evident from the values of coupling constants in the NMR spectroscopic data. The ^{1}H NMR spectra of compounds **5a–j** shows doublets of two protons on the azetidinonic ring between δ 4.99–5.72, with a coupling constant of $J = 5.0$–5.8 Hz indicating *cis* stereochemistry at the *β*-lactam ring system (Scheme 2; Fig. 2).

Biological activity

The diverse biological activities of thiophene and fused derivatives prompted us to test and study the biological activities of some of the newly synthesized products. Many antimicrobial agents have been introduced into therapy; however, the field still needs extensive efforts for the development of new antimicrobial agents to overcome the highly resistant strains of microorganisms. The newly



Scheme 2 Mechanism for the formation of 2-azitidinone (*β*-lactam) derivatives

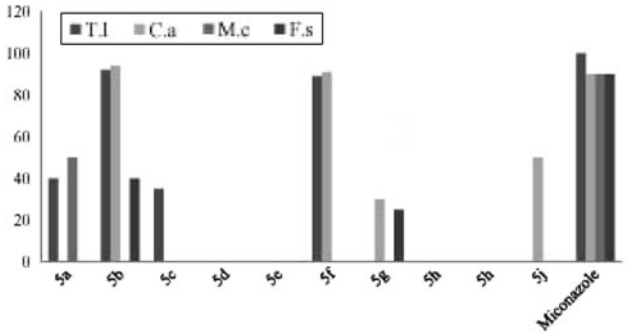


Fig. 2 Antifungal activity of **5a–j**

synthesized compounds **5a–j** were tested in vitro for their antibacterial activity against *Escherichia coli*, *Pseudomonas aeruginosa*, *Bacillus subtillus*, *Staphylococcus aureus*, and *Micrococcus luteus* bacteria by the agar well diffusion method (Linday, 1962). DMSO was used as a control solvent and, chloramphenicol and cefixime as standard drugs. After 24-h incubation at 37°C, the zone of inhibition was measured in mm. The results are depicted in Table 1. The results showed that all compounds were active against *E. coli*. It is worth noting here that compounds **5b** and **5f** exhibited significant activity against *E. coli* and *B. subtillus*. The other compounds showed moderate-to-low activity. The structure–activity relationship (SAR) shows that the presence of substitution at the 2-position (ortho) of the phenyl substituent enhanced the antibacterial action of the compounds (Fig. 1).

Compounds **5a–j** were also screened in vitro for their antifungal activity against four species using the agar plate technique (Collins, 1967). The linear growth of the fungus was obtained by measuring the diameter of the fungal colony after 7 days. The amount of growth inhibition in each case was calculated as percentage inhibition. The results shown in Table 2 indicated that compounds **5b** and **5f** exhibited significant activity against *Trichphyton longifusus* and *Candida albicans*, respectively. It is worth noting that compounds **5b** and **5f** exhibited significant (maximum) antibacterial and antifungal activities, possibly because of the presence of substitution at the 2-position (ortho) of the phenyl substituent, in addition to the azetidinone moiety (Fig. 2).

Conclusions

In the present article, we report the synthesis, spectral studies, stereochemistry, and anti-microbial activity of a novel series of novel benzo[*b*]thiophenes comprising *β*-lactam nucleus. The ^{1}H NMR studies evidenced the formation of *cis* isomers. The preliminary in vitro biological activities of the title compounds 2-(3-(2,4-dichlorophenoxy)-2-(aryl)-4-oxoazetidin-1-yl)-5-(2-(5-chloro-3-methyl-1-phenyl-1*H*-pyrazol-4-yl)

Table 1 Antibacterial activity of **5a–j**

Compound	R	E.c	P.a	B.s	S.a	M.l
5a	Phenyl	14.19	11.65	11.70	–	–
5b	2-Chlorophenyl	17.81	10.56	18.70	11.28	13.09
5c	4-Chlorophenyl	13.90	11.20	12.36	10.56	–
5d	3,4-Dichlorophenyl	12.00	10.85	11.25	–	–
5e	4-(N,N-Dimethyl)phenyl	14.56	–	–	–	–
5f	2-Hydroxyphenyl	17.55	11.56	18.86	12.35	–
5g	4-Methoxyphenyl	15.56	11.90	12.46	11.26	–
5h	3-Hydroxy-4-methoxyphenyl	13.69	–	–	–	–
5i	4-Nitrophenyl	13.96	12.10	11.23	–	–
5j	3,4,5-Trimethoxyphenyl	12.95	11.68	11.61	10.59	–
Chlorampenicol	–	17.00	19.60	18.80	16.45	17.20
Cefixime (Standard)	–	30.00	17.78	28.70	36.12	34.11

Zone diameter of growth inhibition (mm) after 24 h, <10 mm (−), Concentration 1 mg/mL in DMSO. Microorganisms selected are as follows: E.c, *Escherichia coli*; P.a, *Pseudomonas aeruginosa*; B.s, *Bacillus subtillus*; S.a, *Staphylococcus aureus*; M.l, *Micrococcus luteus*

Table 2 Antifungal activity of **5a–j**

Compound	R	T.l	C.a	M.c	F.s
5a	Phenyl	40	–	50	–
5b	2-Chlorophenyl	92	94	–	40
5c	4-Chlorophenyl	35	–	–	–
5d	3,4-Dichlorophenyl	–	–	–	–
5e	4-(*N*,*N*-Dimethyl)phenyl	–	–	–	–
5f	2-Hydroxyphenyl	89	91	–	–
5g	4-Methoxyphenyl	–	30	–	25
5h	3-Hydroxy-4-methoxyphenyl	–	–	–	–
5i	4-Nitrophenyl	–	–	–	–
5j	3,4,5-Trimethoxyphenyl	–	50	–	–
Miconazole (Standard)	–	100	90	90	90

Conc. of sample 200 μg/mL in DMSO at 27°C, Incubation period 7 days. Microorganisms selected are as follows: T.l, *Trichphyton longifusus*; C.a, *Candida albicans*; M.c, *Microsporum canis*; F.s, *Fusarium solani*

vinyl)-6,7-dihydro-7,7-dimethylbenzo[*b*]thiophene-3-carbonitriles revealed that compounds **5b** and **5f** exhibited significant (maximum) antibacterial and antifungal activities. In summary, we have identified a novel series of benzo[*b*]thiophene derivatives comprising β-lactam nucleus, which may develop into the potential class of antimicrobial agents.

Experimental

General

All the research chemicals were purchased from Sigma-Aldrich and used as such for the reactions. Reactions were monitored by thin-layer chromatography (TLC) on pre-coated silica gel GF254 plates from E-Merck Co, and compounds visualized by exposure to UV. Melting points were determined in open capillaries and are uncorrected. The IR spectra were recorded on Nicolet Impact 410 FT IR spectrophotometer using KBr pellets. ^{1}H and ^{13}C NMR spectra were recorded on Bruker 300-MHz FT NMR spectrometer in $CDCl_3$ with TMS as internal standard. Mass spectrum was recorded on Thermo-Finnigan-MAT, Bremen (Model MAT8200) spectrometer, and elemental analysis was carried out using Heraus CHN rapid analyzer.

Chemistry

*Synthesis of 2-(3,5,5-trimethylcyclohex-2-enylidene)malononitrile (**1**)*

A solution of equimolar quantities of isophorone (0.10 mmol) and malononitrile (0.10 mmol) were refluxed in dry ethanol in the presence of piperidyl acetate as a catalyst (2–3 drops) for 3 h. The product separated out on cooling was filtered, washed with cold ethanol, dried, and recrystallized from petroleum ether. Yield: 63%, m.p. 76–78°C.

*Synthesis of 2-(3-((E)-2-(5-chloro-3-methyl-1-phenyl-1H-pyrazol-4-yl)vinyl)-5,5-dimethylcyclohex-2-enylidene)malononitrile (**2**)*

Equimolar quantities of 2-(3,5,5-trimethylcyclohex-2-enylidene)malononitrile **1** (0.10 mmol) and 5-chloro-3-methyl-1-phenyl-1*H*-pyrazole-4-carbaldehyde (0.10 mmol) was refluxed in dry ethanol in the presence of piperidyl acetate as a catalyst (2–3 drops) for 5 h. The product separated out on cooling was filtered, dried and recrystallized from absolute alcohol. Yield = 83%, m.p. 156–158°C. IR

(KBr) cm^{-1}: 3045, 2946, 2872, 2232, 1661, 1599, 1540, 692. ^1H NMR (300 MHz, $CDCl_3$): 1.09 (s, 6H, CH_3), 1.68 (s, 4H, CH_2), 2.34 (s, 3H, CH_3), 6.03 (s, 1H, CH), 6.32 (d, 1H, CH, $J = 14.6$ Hz), 6.48 (d, 1H, CH, $J = 14.4$ Hz), 7.37-7.88 (m, 5H, Ar–H); ^{13}C NMR ($CDCl_3$): 10.1, 11.4, 28.3, 40.7, 43.1, 45.4, 81.7, 112.6, 120.1, 126.1, 127.9, 129.6, 130.9, 136.9, 139.8, 140.7, 149.5, 179.8. MS (m/z): 388; Anal. Calcd. for $C_{23}H_{21}ClN_4$: C, 71.03; H, 5.44; N, 14.41. Found: C, 70.82; H, 5.50; N, 14.26.

*Synthesis of 2-amino-5-((E)-2-(5-chloro-3-methyl-1-phenyl-1H-pyrazol-4-yl)vinyl)-6,7-dihydro-7, 7-dimethylbenzo[b]thiophene-3-carbonitrile (**3**)*

2-(3-((*E*)-2-(5-chloro-3-methyl-1-phenyl-1*H*-pyrazol-4-yl) vinyl)-5,5-dimethylcyclohex-2-enylidene)malononitrile **2** (0.10 mmol) was stirred at 60°C with sulfur (0.10 mmol) in the presence of morpholine (5 ml) in ethanol (20 ml) for 6 h. The mixture was cooled, poured onto crushed ice, and neutralized with dilute HCl. The product obtained was filtered, dried, and recrystallized from absolute alcohol. Yield = 86%, m.p. 206–208°C. IR (KBr) cm^{-1}: 3288, 3056, 2954, 2862, 2221, 1656, 1589, 1552, 692. ^1H NMR (300 MHz, $CDCl_3$): 1.31 (s, 6H, CH_3), 2.12 (s, 2H, CH_2), 2.62 (s, 3H, CH_3), 5.12 (s, 2H, NH_2), 6.11 (s, 1H, CH), 6.31 (d, 1H, CH, $J = 14.5$ Hz), 6.48 (d, 1H, CH, $J = 14.4$ Hz), 7.12–8.18 (m, 5H, Ar–H); ^{13}C NMR ($CDCl_3$): 11.0, 30.2, 30.9, 50.1, 107.9, 110.2, 114.9, 120.1, 122.4, 126.2, 129.1, 131.1, 133.2, 134.8, 137.0, 139.6, 140.8, 146.1, 149.2. MS (m/z): 420; Anal. Calcd. for $C_{23}H_{21}ClN_4S$: C, 65.62; H, 5.03; N, 13.31. Found: C, 65.48; H, 4.88; N, 13.16.

*General procedure for the synthesis of 2-(arylideneamino)-5-(2-(5-chloro-3-methyl-1-phenyl-1H-pyrazol-4-yl)vinyl)-6,7-dihydro-7,7-dimethylbenzo[b]thiophene-3-carbonitriles (**4a–j**)*

A mixture of 2-amino-5-(2-(5-chloro-3-methyl-1-phenyl-1*H*-pyrazol-4-yl)vinyl)-6,7-dihydro-7,7-dimethylbenzo[*b*]thiophene-3-carbonitrile **3** (0.10 mmol) and appropriate aldehyde (0.10 mmol) was refluxed in absolute ethanol (15 ml) for 2–3 h. The solid mass that separated out was filtered, washed with water, and crystallized from absolute ethanol to give the preferred product (**4a–j**).

*2-(Benzylideneamino)-5-(2-(5-chloro-3-methyl-1-phenyl-1H-pyrazol-4-yl)vinyl)-6,7-dihydro-7, 7-dimethylbenzo[b]thiophene-3-carbonitrile (**4a**)*

Yield = 76%, m.p. 255–257°C. IR (KBr) cm^{-1}: 3051, 2945, 2854, 2214, 1646, 1589, 1552, 745, 701. ^1H NMR (300 MHz, $CDCl_3$): 1.29 (s, 6H, CH_3), 2.02 (s, 2H, CH_2), 2.53 (s, 3H, CH_3), 5.22 (s, 1H, CH), 6.19 (s, 1H, CH), 6.29 (d, 1H, CH), 6.40 (d, 1H, CH), 8.09 (s, 1H, CH), 7.22–8.28 (m, 10H, Ar–H); ^{13}C NMR ($CDCl_3$): 11.2, 30.2, 30.6, 49.7, 107.9, 110.1, 115.2, 120.1, 122.7, 126.2, 128.7, 129.1, 129.5, 130.0, 131.2, 132.9, 133.6, 134.9, 137.1, 139.9, 140.7, 149.9, 162.3. MS (m/z): 508; Anal. Calcd. for $C_{30}H_{25}ClN_4S$: C, 70.78; H, 4.95; N, 11.12. Found: C, 70.48; H, 4.64; N, 10.70.

*2-(2-Chlorobenzylideneamino)-5-(2-(5-chloro-3-methyl-1-phenyl-1H-pyrazol-4-yl)vinyl)-6,7-dihydro-7, 7-dimethylbenzo[b]thiophene-3-carbonitrile (**4b**)*

Yield = 81%, m.p. 247–249°C. IR (KBr) cm^{-1}: 3043, 2938, 2848, 2204, 1656, 1593, 1549, 740, 699. ^1H NMR (300 MHz, $CDCl_3$): 1.33 (s, 6H, CH_3), 2.14 (s, 2H, CH_2), 2.43 (s, 3H, CH_3), 6.09 (s, 1H, CH), 6.24 (d, 1H, CH), 6.40 (d, 1H, CH), 8.12 (s, 1H, CH), 7.31–8.27 (m, 9H, Ar–H); ^{13}C NMR ($CDCl_3$): 11.4, 30.6, 30.9, 50.1, 108.3, 111.9, 115.1, 120.6, 122.7, 126.1, 126.9, 128.8, 129.5, 131.1, 131.2, 132.8, 133.3, 133.6, 134.2, 135.4, 137.3, 139.8, 140.4, 146.2, 150.3, 158.4, 161.0. MS (m/z): 542; Anal. Calcd. for $C_{30}H_{24}Cl_2N_4S$: C, 66.30; H, 4.45; N, 10.31. Found: C, 66.10; H, 4.26; N, 10.36.

*2-(4-Chlorobenzylideneamino)-5-(2-(5-chloro-3-methyl-1-phenyl-1H-pyrazol-4-yl)vinyl)-6,7-dihydro-7, 7-dimethylbenzo[b]thiophene-3-carbonitrile (**4c**)*

Yield = 83%, m.p. 226–228°C. IR (KBr) cm^{-1}: 3041, 2932, 2851, 2209, 1646, 1599, 1552, 735, 694. ^1H NMR (300 MHz, $CDCl_3$): 1.23 (s, 6H, CH_3), 2.24 (s, 2H, CH_2), 2.33 (s, 3H, CH_3), 6.12 (s, 1H, CH), 6.18 (d, 1H, CH), 6.36 (d, 1H, CH), 8.16 (s, 1H, CH), 7.21–8.37 (m, 9H, Ar–H); ^{13}C NMR ($CDCl_3$): 11.4, 30.5, 30.8, 50.0, 107.9, 111.9, 115.4, 120.3, 123.0, 128.8, 129.3, 130.1, 131.0, 132.1, 132.9, 134.8, 136.2, 137.2, 139.1, 140.9, 147.2, 149.4, 157.4, 162.6. MS (m/z): 542; Anal. Calcd. for $C_{30}H_{24}Cl_2N_4S$: C, 66.30; H, 4.45; N, 10.31. Found: C, 66.10; H, 4.36; N, 10.21.

*2-(3,4-Chlorobenzylideneamino)-5-(2-(5-chloro-3-methyl-1-phenyl-1H-pyrazol-4-yl)vinyl)-6,7-dihydro-7, 7-dimethylbenzo[b]thiophene-3-carbonitrile (**4d**)*

Yield = 78%, m.p. 198–200°C. IR (KBr) cm^{-1}: 3049, 2931, 2848, 2212, 1661, 1590, 1549, 736, 694. ^1H NMR (300 MHz, $CDCl_3$): 1.24 (s, 6H, CH_3), 2.11 (s, 2H, CH_2), 2.31 (s, 3H, CH_3), 6.11 (s, 1H, CH), 6.20 (d, 1H, CH), 6.36 (d, 1H, CH), 8.42 (s, 1H, CH), 7.31–8.27 (m, 8H, Ar–H); ^{13}C NMR (CDCl3): 11.7, 30.3, 49.7, 106.7, 110.7, 116.1, 120.7, 122.9, 125.9, 128.4, 129.6, 130.4, 130.8, 131.7,

132.9, 133.4, 133.7, 135.0, 135.8, 138.1, 139.3, 140.8, 147.1, 150.0, 158.7, 161.4. MS (m/z): 578; Anal. Calcd. for $C_{30}H_{23}Cl_3N_4S$: C, 62.34; H, 4.01; N, 9.69. Found: C, 62.19; H, 4.06; N, 9.57.

*2-(4-(N,N-dimetylbenzylideneamino)-5-(2-(5-chloro-3-methyl-1-phenyl-1H-pyrazol-4-yl)vinyl)-6,7-dihydro-7,7-dimethylbenzo[b]thiophene-3-carbonitrile (**4e**)*

Yield = 67%, m.p. 208–210°C. IR (KBr) cm^{-1}: 3312, 3051, 2934, 2851, 2206, 1656, 1593, 1556, 741, 696. ^1H NMR (300 MHz, $CDCl_3$): 1.18 (s, 6H, CH_3), 2.18 (s, 2H, CH_2), 2.25 (s, 3H, CH_3), 2.90 (s, 6H, CH_3), 6.03 (s, 1H, C), 6.12 (d, 1H, CH), 6.36 (d, 1H, CH), 8.36 (s, 1H, CH), 7.01-8.12 (m, 9H, Ar–H); ^{13}C NMR ($CDCl_3$): 11.1, 30.4, 30.6, 49.9, 105.6, 110.8, 113.8, 115.9, 121.0, 123.0, 124.9, 126.2, 129.8, 130.7, 131.2, 133.4, 135.1, 137.4, 139.4, 146.2, 149.4, 152.3, 157.9, 160.3. MS (m/z): 551; Anal. Calcd. for $C_{32}H_{30}OClN_5S$: C, 69.61; H, 5.48; N, 12.68. Found: C, 69.54; H, 5.32; N, 12.59.

*2-(2-Hydroxybenzylideneamino)-5-(2-(5-chloro-3-methyl-1-phenyl-1H-pyrazol-4-yl)vinyl)-6,7-dihydro-7,7-dimethylbenzo[b]thiophene-3-carbonitrile (**4f**)*

Yield = 69%, m.p. 211–213°C. IR (KBr) cm^{-1}: 3250, 3056, 2929, 2838, 2218, 1655, 1595, 1553, 1112, 742, 696. ^1H NMR (300 MHz, $CDCl_3$): 1.19 (s, 6H, CH_3), 2.09 (s, 2H, CH_2), 2.29 (s, 3H, CH_3), 5.12 (s, 1H, OH), 6.13 (s, 1H, CH), 6.29 (d, 1H, CH), 6.42 (d, 1H, CH), 8.34 (s, 1H, CH), 7.31–8.27 (s, 9H, Ar–H); ^{13}C NMR ($CDCl_3$): 11.3, 31.1, 31.3, 50.1, 105.4, 110.4, 114.8, 115.7, 118.4, 121.0, 121.9, 122.8, 125.8, 126.3, 129.2, 130.1, 131.1, 132.4, 133.1, 136.1, 137.4, 139.4, 140.4, 145.9, 148.9, 158.7, 161.0, 162.0. MS (m/z): 524; Anal. Calcd. for $C_{30}H_{25}ClN_4OS$: C, 68.62; H, 4.80; N, 10.67. Found: C, 68.38; H, 4.81; N, 10.54.

*2-(4-Methoxybenzylideneamino)-5-(2-(5-chloro-3-methyl-1-phenyl-1H-pyrazol-4-yl)vinyl)-6,7-dihydro-7,7-dimethylbenzo[b]thiophene-3-carbonitrile (**4g**)*

Yield = 78%, m.p. 185–187°C. IR (KBr) cm^{-1}: 3050, 2932, 2835, 2214, 1658, 1598, 1563, 1123, 732, 706. ^1H NMR (300 MHz, $CDCl_3$): 1.21 (s, 6H, CH_3), 2.21 (s, 2H, CH_2), 2.36 (s, 3H, CH_3), 3.66 (s, 3H, OCH_3), 6.03 (s, 1H, CH), 6.12 (d, 1H, CH), 6.30 (d, 1H, CH), 6.76 (d, 1H, CH), 8.52 (s, 1H, CH), 7.24–8.32 (m, 5H, Ar–H); ^{13}C NMR ($CDCl_3$): 11.0, 30.8, 31.1, 50.3, 60, 107.6, 111.2, 114.2, 115.4, 120.0, 122.1, 126.0, 126.2, 129.2, 130.4, 131.4, 133.7, 134.8, 137.2, 139.4, 140.7, 149.6, 147.0, 159.0, 163.0, 164.4. MS (m/z): 538; Anal. Calcd. for $C_{31}H_{27}ClN_4OS$: C, 69.07; H, 5.05; N, 10.39. Found: C, 68.88; H, 5.00; N, 10.26.

*2-(3-Hydroxy-4-methoxybenzylideneamino)-5-(2-(5-chloro-3-methyl-1-phenyl-1H-pyrazol-4-yl)vinyl)-6,7-dihydro-7,7-dimethylbenzo[b]thiophene-3-carbonitrile (**4h**)*

Yield = 70%, m.p. 226–228°C. IR (KBr) cm^{-1}: 3236, 3044, 2926, 2838, 2204, 1652, 1592, 1559, 1131, 722, 702. ^1H NMR (300 MHz, $CDCl_3$): 1.19 (s, 6H, CH_3), 2.14 (s, 2H, CH_2), 2.33 (s, 3H, CH_3), 3.52 (s, 3H, OCH_3), 5.32 (s, 1H, OH), 6.04 (d, 1H, CH), 6.12 (d, 1H, CH), 8.32 (s, 1H, CH), 7.20–8.24 (m, 8H, Ar–H); ^{13}C NMR ($CDCl_3$): 11.4, 30.6, 30.9, 54.9, 106.7, 111.2, 115.2, 115.4, 115.9, 120.3, 122.7, 122.9, 126, 127.9, 129.9, 131.0, 133.6, 134.7, 137.2, 139.5, 140.7, 144.9, 146.3, 150.0, 152.4, 158.9, 160.3. MS (m/z): 554; Anal. Calcd. for $C_{31}H_{27}ClN_4O_2S$: C, 67.08; H, 4.90; N, 10.09. Found: C, 66.89; H, 4.84; N, 10.02.

*2-(4-Nitrobenzylideneamino)-5-(2-(5-chloro-3-methyl-1-phenyl-1H-pyrazol-4-yl)vinyl)-6,7-dihydro-7,7-dimethylbenzo[b]thiophene-3-carbonitrile (**4i**)*

Yield = 87%, m.p. 157–159°C. IR (KBr) cm^{-1}: 3042, 2926, 2831, 2218, 1654, 1599, 1569, 1119, 745, 712. ^1H NMR (300 MHz, $CDCl_3$): 1.12 (s, 6H, CH_3), 2.14 (s, 2H, CH_2), 2.29 (s, 3H, CH_3), 6.11 (s, 1H, CH), 6.19 (d, 1H, CH), 6.24 (d, 1H, CH), 6.70 (s, 2H, CH), 7.12 (d, 2H, CH), 8.36 (s, 1H, CH), 7.30–8.45 (m, 5H, Ar–H); ^{13}C NMR ($CDCl_3$): 11.7, 30.2, 30.9, 49.4, 170.6, 109.9, 114.9, 121.0, 121.3, 122.4, 126.1, 129.1, 130.2, 131.8, 132.9, 134.9, 137.3, 139.6, 139.8, 140.4, 146.4, 149.4, 150.4, 159.4. MS (m/z): 569; Anal. Calcd. for $C_{30}H_{24}ClN_5O_3S$: C, 63.21; H, 4.24; N, 12.29. Found: C, 63.10; H, 4.09; N, 12.27.

*2-(3,4,5-Trimethoxybenzylideneamino)-5-(2-(5-chloro-3-methyl-1-phenyl-1H-pyrazol-4-yl)vinyl)-6,7-dihydro-7,7-dimethylbenzo[b]thiophene-3-carbonitrile (**4j**)*

Yield = 72%, m.p. 266–268°C. IR (KBr) cm^{-1}: 3048, 2931, 2844, 2216, 1651, 1602, 1572, 1121, 739, 709. ^1H NMR (300 MHz, $CDCl_3$): 1.18 (s, 6H, CH_3), 2.27 (s, 2H, CH_2), 2.36 (s, 3H, CH_3), 3.65 (s, 9H, OCH_3), 6.04 (s, 1H, CH), 6.21 (d, 1H, CH), 6.32 (d, 1H, CH), 6.54 (d, 1H, CH), 8.46 (s, 1H, CH), 7.19–8.15 (m, 5H, Ar–H); ^{13}C NMR ($CDCl_3$): 10.9, 31.0, 31.4, 50.1, 56.2, 56.6, 106.3, 107.4, 110.4, 115.2, 120.1, 122.7, 126.2, 128.4, 129.2, 131.1, 132.9, 134.8, 137.2, 139.4, 140.3, 141.2, 146.2, 149.4, 150.7, 157.9, 161.4. MS (m/z): 598; Anal. Calcd. for

$C_{33}H_{31}ClN_4O_3S$: C, 66.15; H, 5.22; N, 9.35. Found: C, 66.00; H, 5.14; N, 9.30.

*General procedure for the synthesis of 2-(3-(2,4-dichlorophenoxy)-2-(aryl)-4-oxoazetidin-1-yl)-5-(2-(5-chloro-3-methyl-1-phenyl-1H-pyrazol-4-yl)vinyl)-6,7-dihydro-7,7-dimethylbenzo[b]thiophene-3-carbonitriles (**5a–j**)*

To a well-stirred solution of the 2-(4-arylideneamino)-5-(-2-(5-chloro-3-methyl-1-phenyl-1*H*-pyrazol-4-yl)vinyl)-6,7-dihydro-7,7-dimethylbenzo[*b*]thiophene-3-carbonitrile (0.10 mmol), 2,4-dichlorophenoxy acetic acid (0.10 mmol) and triethylamine (0.25 mmol) in dry dioxane (30 ml), a solution of benzene sulfonyl chloride (0.10 mmol) in dry dioxane was added dropwise at 0–5°C over a period of 45 min. The stirring was continued at room temperature for a specific period and the reaction mass was kept at room temperature for 3 days. The reaction mass was poured onto crushed ice, filtered, dried, and recrystallized from dioxane–methanol (3:1) to yield the preferred product.

*2-(3-(2,4-Dichlorophenoxy)-2-(phenyl)-4-oxoazetidin-1-yl)-5-(2-(5-chloro-3-methyl-1-phenyl-1H-pyrazol-4-yl)vinyl)-6,7-dihydro-7,7-dimethylbenzo[b]thiophene-3-carbonitrile (**5a**)*

Yield = 62%, m.p. 220–222°C. IR (KBr) cm^{-1}: 3105, 2974, 2868, 2854, 2210, 1732, 1684, 1436, 1263, 758, 644, 616. ^1H NMR (300 MHz, $CDCl_3$): 1.41 (s, 6H, CH_3), 2.30 (s, 2H, CH_2), 2.80 (s, 3H, CH_3), 5.11 (d, 1H, CH, $J = 5.3$ Hz), 5.72 (d, 1H, CH, $J = 5.5$ Hz), 6.41 (s, 1H, CH), 6.50 (d, 1H, CH), 6.72 (d, 1H, CH), 7.01–8.19 (m, 13H, Ar–H); ^{13}C NMR ($CDCl_3$): 11.4, 30.3, 30.7, 49.7, 60.1, 65.1, 86.4, 107.6, 115.1, 118.3, 120.3, 123.2, 124.5, 125.3, 126.0, 126.9, 127.2, 127.5, 128.4, 129.5, 130.9, 131.4, 132.8, 134.1, 139.6, 140.4, 143.1, 145.7, 147.2, 149.0, 149.7, 166.6. MS (m/z): 712; Anal. Calcd. for $C_{38}H_{29}Cl_3N_4O_2S$: C, 64.09; H, 4.10; N, 7.87. Found: C, 64.00; H, 4.02; N, 7.80.

*2-(3-(2,4-Dichlorophenoxy)-2-(2-chlorophenyl)-4-oxoazetidin-1-yl)-5-(2-(5-chloro-3-methyl-1-phenyl-1H-pyrazol-4-yl)vinyl)-6,7-dihydro-7,7-dimethylbenzo[b]thiophene-3-carbonitrile (**5b**)*

Yield = 59%, m.p. 260–262°C. IR (KBr) cm^{-1}: 3103, 2968, 2861, 2214, 1735, 1679, 1423, 1259, 762, 639, 623. ^1H NMR (300 MHz, $CDCl_3$): 1.36 (s, 6H, CH_3), 2.23 (s, 2H, CH_2), 2.73 (s, 3H, CH_3), 4.99 (d, 1H, CH, $J = 5.0$ Hz), 5.62 (d, 1H, CH, $J = 5.2$ Hz), 6.39 (s, 1H, CH), 6.49 (d, 1H, CH), 6.65 (d, 1H, CH), 7.11–8.19 (m, 12H, Ar–H); ^{13}C NMR ($CDCl_3$): 11.2, 30.2, 30.7, 50.1, 50.7, 65.0, 86.0, 107.4, 115.2, 117.4, 120.4, 123.6, 124, 125.6, 126.2, 126.8, 127.4, 127.8, 128.0, 128.4, 128.8, 129.2, 131.2, 132.1, 132.7, 133.2, 134.1, 140.0, 140.9, 143.4, 146.0, 147.2, 149.0, 149.8, 167.0. MS (m/z): 746; Anal. Calcd. for $C_{38}H_{28}Cl_4N_4O_2S$: C, 61.14; H, 3.78; N, 7.50. Found: C, 61.24; H, 3.64; N, 7.26.

*2-(3-(2,4-Dichlorophenoxy)-2-(4-chlorophenyl)-4-oxoazetidin-1-yl)-5-(2-(5-chloro-3-methyl-1-phenyl-1H-pyrazol-4-yl)vinyl)-6,7-dihydro-7,7-dimethylbenzo[b]thiophene-3-carbonitrile (**5c**)*

Yield = 57%, m.p. 297–299°C. IR (KBr) cm^{-1}: 3098, 2973, 2869, 2218, 1741, 1686, 1429, 1261, 759, 656, 628. ^1H NMR (300 MHz, $CDCl_3$): 1.40 (s, 6H, CH_3), 2.39 (s, 2H, CH_2), 2.81 (s, 3H, CH_3), 5.22 (d, 1H, CH, $J = 5.3$ Hz), 5.79 (d, 1H, CH, $J = 5.5$ Hz), 6.35 (s, 1H, CH), 6.45 (d, 1H, CH), 6.66 (d, 1H, CH), 7.26–8.29 (m, 12H, Ar–H); ^{13}C NMR ($CDCl_3$): 11.3, 30.2, 30.9, 49.7, 60.4, 87.1, 95.0, 108.4, 115.2, 117.3, 120.4, 123.6, 124.2, 125.2, 125.9, 126.7, 126.9, 127.8, 128.0, 129.6, 130.2, 131.1, 131.4, 133.2, 134.2, 134.6, 139.8, 140.4, 145.0, 146.0, 147.6, 149.2, 149.8, 166.8. MS (m/z): 746; Anal. Calcd. for $C_{38}H_{28}Cl_4N_4O_2S$: C, 61.14; H, 3.78; N, 7.50. Found: C, 61.14; H, 3.54; N, 7.26.

*2-(3-(2,4-Dichlorophenoxy)-2-(3,4-chlorophenyl)-4-oxoazetidin-1-yl)-5-(2-(5-chloro-3-methyl-1-phenyl-1H-pyrazol-4-yl)vinyl)-6,7-dihydro-7,7-dimethylbenzo[b]thiophene-3-carbonitrile (**5d**)*

Yield = 63%, m.p. 218–220°C. IR (KBr) cm^{-1}: 3091, 2980, 2860, 2208, 1735, 1689, 1442, 1256, 768, 643, 619. ^1H NMR (300 MHz, $CDCl_3$): 1.35 (s, 6H, CH_3), 2.32 (s, 2H, CH_2), 2.71 (s, 3H, CH_3), 5.18 (d, 1H, CH, $J = 5.4$ Hz), 5.69 (d, 1H, CH, $J = 5.8$ Hz), 6.39 (s, 1H, CH), 6.41 (d, 1H, CH), 6.69 (d, 1H, CH), 7.04–8.23 (m, 11H, Ar–H); ^{13}C NMR ($CDCl_3$): 11.4, 30.2, 30.6, 49.9, 60.6, 87.0, 95.1, 107.6, 115.6, 117.8, 120.4, 123.4, 124.2, 124.9, 126.0, 126.2, 127.1, 127.4, 128.1, 129.2, 130.0, 131.3, 131.5, 132.9, 133.3, 134.3, 139.8, 140.7, 142.9, 146.1, 147.2, 149.0, 149.7, 166.4. MS (m/z): 780; Anal. Calcd. for $C_{38}H_{27}Cl_5N_4O_2S$: C, 58.44; H, 3.48; N, 7.17. Found: C, 58.24; H, 3.33; N, 7.12.

*2-(3-(2,4-Dichlorophenoxy)-2-(4-(N,N-dimethyl)phenyl)-4-oxoazetidin-1-yl)-5-(2-(5-chloro-3-methyl-1-phenyl-1H-pyraβol-4-yl)vinyl)-6,7-dihydro-7,7-dimethylbenzo[b]thiophene-3-carbonitrile (**5e**)*

Yield = 61%, m.p. 198–200°C. IR (KBr) cm^{-1}: 3107, 2972, 2856, 2212, 1740, 1676, 1450, 1332, 1260, 769, 640, 610. ^1H NMR (300 MHz, $CDCl_3$): 1.34 (s, 6H, CH_3), 2.26 (s, 2H, CH_2), 2.80 (s, 3H, CH_3), 3.12 (s, 6H, CH_3), 5.26 (d, 1H, CH,

$J = 5.3$ Hz), 5.72 (d, 1H, CH, $J = 5.7$ Hz), 6.36 (s, 1H, CH), 6.46 (d, 1H, CH), 6.61 (d, 1H, CH), 7.18–8.29 (m, 12H, Ar–H); ^{13}C NMR ($CDCl_3$): 11.0, 30.2, 30.6, 40.4, 49.7, 60.2, 87.3, 94.7, 107.3, 112.9, 115.3, 116.9, 120.6, 123.4, 124.4, 125.4, 126.2, 127.0, 127.3, 127.6, 127.9, 129.7, 131.2, 131.4, 132.9, 133.1, 134.5, 140.1, 140.7, 146.0, 147.2, 147.6, 149.4, 149.8, 166.2. MS (m/z): 755; Anal. Calcd. for $C_{40}H_{34}Cl_3N_5O_2S$: C, 63.62; H, 4.54; N, 9.27. Found: C, 63.46; H, 4.50; N, 9.21.

*2-(3-(2,4-Dichlorophenoxy)-2-(2-hydroxyphenyl)-4-oxoazetidin-1-yl)-5-(2-(5-chloro-3-methyl-1-phenyl-1H-pyrazol-4-yl)vinyl)-6,7-dihydro-7,7-dimethylbenzo[b]thiophene-3-carbonitrile (**5f**)*

Yield = 57%, m.p. 171–173°C. IR (KBr) cm^{-1}: 3290, 3108, 2976, 2872, 2213, 1729, 1687, 1439, 1260, 766, 649, 612. ^{1}H NMR (300 MHz, $CDCl_3$): 1.36 (s, 6H, CH_3), 2.24 (s, 2H, CH_2), 2.92 (s, 3H, CH_3), 5.11 (s, 1H, OH), 5.19 (d, 1H, CH, $J = 5.4$ Hz), 5.80 (d, 1H, CH, $J = 5.1$ Hz), 6.42 (s, 1H, CH), 6.51 (d, 1H, CH), 6.69 (d, 1H, CH), 7.12–8.42 (m, 12H, Ar–H); ^{13}C NMR ($CDCl_3$): 11.4, 30.3, 30.9, 49.5, 50.4, 86.9, 95.0, 107.6, 115.8, 116.0, 117.4, 119.8, 121.3, 123.3, 124.4, 125.0, 126.1, 127.2, 127.8, 128.0, 128.3, 129.7, 130.8, 131.1, 131.4, 133.2, 134.6, 139.8, 140.7, 146.0, 147.2, 150.0, 154.3, 156.3, 166.4. MS (m/z): 728; Anal. Calcd. for $C_{38}H_{29}Cl_3N_4O_3S$: C, 62.69; H, 4.01; N, 7.70. Found: C, 62.48; H, 4.20; N, 7.55.

*2-(3-(2,4-Dichlorophenoxy)-2-(4-methoxyphenyl)-4-oxoazetidin-1-yl)-5-(2-(5-chloro-3-methyl-1-phenyl-1H-pyrazol-4-yl)vinyl)-6,7-dihydro-7,7-dimethylbenzo[b]thiophene-3-carbonitrile (**5g**)*

Yield = 68%, m.p. 175–177°C. IR (KBr) cm^{-1}: 3103, 2970, 2871, 2220, 1733, 1680, 1442, 1268, 756, 649, 621. ^{1}H NMR (300 MHz, $CDCl_3$): 1.21 (s, 6H, CH_3), 2.21 (s, 2H, CH_2), 2.81 (s, 3H, CH_3), 3.79 (s, 3H, OCH_3), 5.31 (d, 1H, CH, $J = 5.0$ Hz), 5.81 (d, 1H, CH, $J = 5.4$ Hz), 6.46 (s, 1H, CH), 6.56 (d, 1H, CH), 6.69 (d, 1H, CH), 7.02–8.16 (m, 12H, Ar–H); ^{13}C NMR ($CDCl_3$): 11.3, 30.2, 31.0, 49.8, 54.9, 61.2, 87.1, 95.2, 107.4, 112.9, 115.6, 117.4, 120.3, 124.0, 124.4, 125.3, 126.1, 127.6, 127.9, 128.2, 129.6, 131.2, 131.8, 133.3, 134.7, 135.9, 140.0, 140.8, 144.8, 147.2, 148.9, 149.8, 158.6, 166.7. MS (m/z): 742; Anal. Calcd. for $C_{39}H_{31}Cl_3N_4O_3S$: C, 63.12; H, 4.21; N, 7.55. Found: C, 62.99; H, 4.04; N, 7.46.

*2-(3-(2,4-Dichlorophenoxy)-2-(3-hydroxy-4-methoxyphenyl)-4-oxoazetidin-1-yl)-5-(2-(5-chloro-3-methyl-1-phenyl-1H-pyrazol-4-yl)vinyl)-6,7-dihydro-7,7-dimethylbenzo[b]thiophene-3-carbonitrile (**5h**)*

Yield = 64%, m.p. 201–203°C. IR (KBr) cm^{-1}: 3308, 3111, 2972, 2838, 2874, 2212, 1742, 1684, 1448, 1251, 761, 626. ^{1}H NMR (300 MHz, $CDCl_3$): 1.46 (s, 6H, CH_3), 2.24 (s, 2H, CH_2), 2.76 (s, 3H, CH_3), 3.81 (s, 1H, OCH_3), 5.12 (d, 1H, OH), 5.32 (d, 1H, CH, $J = 5.2$ Hz), 5.71 (s, 1H, CH, $J = 5.4$ Hz), 6.32 (s, 1H, CH), 6.50 (d, H, CH), 6.61 (d, H, CH), 7.12–8.329 (s, 11H, Ar–H); ^{13}C NMR ($CDCl_3$): 11.6, 30.2, 30.7, 49.9, 57.1, 62.3, 86.9, 95.0, 107.3, 113.2, 115.4, 115.6, 117.3, 120.0, 120.4, 123.7, 124.2, 125.3, 126.6, 127.2, 127.7, 129.6, 131.1, 131.4, 133.3, 134.7, 137.8, 139.6, 140.4, 145.8, 147.6, 149.0, 149.2, 149.7, 165.7. MS (m/z): 758; Anal. Calcd. for $C_{39}H_{31}Cl_3N_4O_4S$: C, 61.79; H, 4.12; N, 7.39. Found: C, 61.50; H, 4.22; N, 7.29.

*2-(3-(2,4-Dichlorophenoxy)-2-(4-nitrophenyl)-4-oxoazetidin-1-yl)-5-(2-(5-chloro-3-methyl-1-phenyl-1H-pyrazol-4-yl)vinyl)-6,7-dihydro-7,7-dimethylbenzo[b]thiophene-3-carbonitrile (**5i**)*

Yield = 62%, m.p. 181–183°C. IR (KBr) cm^{-1}: 3099, 2969, 2866, 2211, 1732, 1674, 1438, 1265, 1342, 1265, 749, 640, 612. ^{1}H NMR (300 MHz, $CDCl_3$): 1.33 (s, 6H, CH_3), 2.19 (s, 2H, CH_2), 2.80 (s, 3H, CH_3), 5.22 (d, 1H, CH, $J = 5.2$ Hz), 5.54 (d, 1H, CH, $J = 5.2$ Hz), 6.31 (s, 1H, CH), 6.46 (d, 1H, CH), 6.81 (d, 1H, CH), 7.43–8.69 (m, 12H, Ar–H); ^{13}C NMR ($CDCl_3$): 11.2, 30.3, 30.8, 50.1, 60.9, 87.0, 95.1, 106.9, 115.8, 117.1, 120.1, 120.8, 124.0, 124.3, 125.1, 126.2, 127.4, 127.7, 127.9, 129.3, 131.2, 131.6, 133.1, 134.6, 139.8, 140.8, 146.2, 146.9, 147.3, 149.1, 149.7, 166.0. MS (m/z): 757; Anal. Calcd. for $C_{38}H_{28}Cl_3N_5O_4S$: C, 60.28; H, 3.73; N, 9.25. Found: C, 59.28; H, 4.13; N, 9.45.

*2-(3-(2,4-Dichlorophenoxy)-2-(3,4,5-methoxyphenyl)-4-oxoazetidin-1-yl)-5-(2-(5-chloro-3-methyl-1-phenyl-1H-pyrazol-4-yl)vinyl)-6,7-dihydro-7,7-dimethylbenzo[b]thiophene-3-carbonitrile (**5j**)*

Yield = 58%, m.p. 231–233°C. IR (KBr) cm^{-1}: 3088, 2964, 2861, 2210, 1736, 1671, 1446, 1243, 756, 640, 623. ^{1}H NMR (300 MHz, $CDCl_3$): 1.49 (s, 6H, CH_3), 2.40 (s, 2H, CH_2), 2.72 (s, 3H, CH_3), 3.72 (s, 9H, OCH_3), 5.31 (d, 1H, CH, $J = 5.3$ Hz), 5.70 (d, 1H, CH, $J = 5.1$ Hz), 6.12 (s, 1H, CH), 6.29 (d, 1H, CH), 6.56 (d, 1H, CH), 6.98–7.67 (m, 10H, Ar–H); ^{13}C NMR ($CDCl_3$): 11.4, 30.2, 30.6, 49.6, 56.5, 56.8, 61.2, 94.5, 103.0, 104.5, 108.3, 115.1, 117.1, 120.4, 123.5, 124.4, 125.3, 126.1, 127.1, 127.4, 129.1, 131.0, 131.4, 133.3, 134.1, 137.4, 137.5, 139.5, 140.4, 145.7, 147.1, 149.3, 150.3, 165.3. MS (m/z): 802; Anal. Calcd. for $C_{41}H_{35}Cl_3N_4O_5S$: C, 61.39; H, 4.40; N, 6.98. Found: C, 61.09; H, 4.16; N, 7.08.

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