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MEDICINAL CHEMISTRY RESEARCH

ORIGINAL RESEARCH

Exploration of antimicrobial potential of pyrazolo[3,4-*b*]pyridine scaffold bearing benzenesulfonamide and trifluoromethyl moieties

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Abstract The synthesis and biological evaluation of a library of thirty differently substituted pyrazolo[3,4-*b*]pyridines bearing benzenesulfonamide moiety at position-1 and trifluoromethyl group at position-4 are reported. Fused heterocyclic system present in the target compounds (**5a–j**, **6a–j**, and **7a–j**) was constructed by refluxing various 5-aminopyrazoles (**3a–c**) with differently substituted trifluoromethyl-β-diketones (**4a–j**) in glacial acetic acid. All the target compounds (**5–7**) were evaluated for their in vitro antibacterial activity against four pathogenic bacterial strains namely, *Staphylococcus aureus*, *Bacillus subtilis* (Gram-positive), *Escherichia coli*, *Pseudomonas aeruginosa* (Gram-negative) and in vitro antifungal activity against two pathogenic fungal yeasts namely, *Saccharomyces cerevisiae* and *Candida albicans*.

Keywords Pyrazolo[3,4-*b*]pyridines · Benzenesulfonamide · Trifluoromethyl-β-diketones · Antibacterial activity · Antifungal activity

Introduction

Fused heterocycles have emerged as prime pharmaceutical targets these days because of their abundant occurrence in natural as well as synthetic bioactive molecules such as β-lactam in antibiotics penicillins and cephalosporins, quinoline in antimalarials, porphyrin in haemoglobin and chlorophyll, indole in amino acid tryptophan and neurotransmitter serotonin, etc. (Blass, 2012; Chen *et al.*, 2011). Pyrazolo[3,4-*b*]pyridine ring system is an important member of the family of fused heterocycles which has shown promise in designing new pharmaceuticals with better pharmacological profiles. This fused system is associated with diverse biological activities such as antimicrobial (Foks *et al.*, 2005; Leal *et al.*, 2008; El-Sayad, 2009; Parekh and Maheria, 2012), anti-inflammatory (Bharate *et al.*, 2004), analgesic (Menegatti *et al.*, 2006), antimalarial (Menezes *et al.*, 2002), antichagasic (Dias *et al.*, 2007), antileishmanial (Mello *et al.*, 2004), anxiolytic (Bare *et al.*, 1989), antiviral (Bernardino *et al.*, 2007), antidiabetic (Hohn *et al.*, 1973), antitumor (Lin *et al.*, 2007; Hamama *et al.*, 2012), sedative/hypnotic (Menegatti *et al.*, 2006), etc. This nucleus is also known for better enzymatic inhibitory activities such as cyclin-dependant kinases (CDK) (Misra *et al.*, 2003a, 2003b), glycogen synthase kinase-3 (GSK-3) (Witherington *et al.*, 2003a, b), phosphodiesterase 4 (PDE4) (Hamblin *et al.*, 2008), HIV-1 integrase (Wu *et al.*, 2007), etc. It is an established fact that the incorporation of fluorine in many heterocyclic systems increases lipophilicity, thus enhancing the rates of absorption as well as transportation in vivo and hence making the fluoro compounds suitable for drug formulation (Ojima, 2009). Trifluoromethyl (CF_3) group has been found to be one of the most lipophilic of all the substituents. It is well known in the literature that in general, increased lipophilicity makes the partition/permeability of a bioactive molecule into the bacterial as well fungal cell membrane much higher and thus tends to increase the efficacy of a drug (Rezaee *et al.*, 2009). Besides increasing lipophilicity, introduction of a trifluoromethyl moiety as well as its replacement with an existing functional group can alter the physical properties as well as biological

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activities of the parent compound in dramatic ways, e.g. acidity, polarizability, enhanced hydrophobic binding, stability against metabolic oxidation, etc. (Schlosser, 2006; Purser *et al.*, 2008). All these findings make CF_3 bearing aromatics and heteroaromatics as increasingly attractive targets in search of novel pharmaceuticals and thus enjoy a special position in pharmaceutical as well as agrochemical industries. Celecoxib (selective COX-2 inhibitor), prozac (antidepressant), faslodex (estrogen receptor antagonist), aprepitant (antiemetic), efavirenz (anti-HIV), casodex (anticancer agent), desflurane (inhalation anesthetic), indoxacarb (insecticide) are some of the drugs in the market bearing a trifluoromethyl functionality.

Benzenesulfonamide moiety in combination with various heterocycles has been found to be associated with a diverse range of bioactivities such as antimicrobial (Basanagouda *et al.*, 2010; Turkmen *et al.*, 2011), anti-inflammatory (Penning *et al.*, 1997), anticancer (Ghorab *et al.*, 2010; Al-Said *et al.*, 2011), anti-HIV (Iqbal *et al.*, 2006), etc. A perusal of literature reveals that the synthesis of pyrazolo[3,4-*b*]pyridine ring system containing benzenesulfonamide and trifluromethyl group for evaluation as antimicrobial agents is still in its infancy (Sharma *et al.*, 2011a). Appreciation of these findings coupled with our ongoing interest in the field of pyrazoles and other heterocyclic compounds of potential medicinal interest (Sharma *et al.*, 2010, 2011a, b, 2012a, b; Chandak *et al.*, 2012, 2013; Kumar *et al.*, 2012a, b), we envisioned the synthesis of a library of pyarazolo[3,4-*b*]pyridines bearing benzenesulfonamide and trifluoromethyl moieties for their evaluation as antibacterial and antifungal agents.

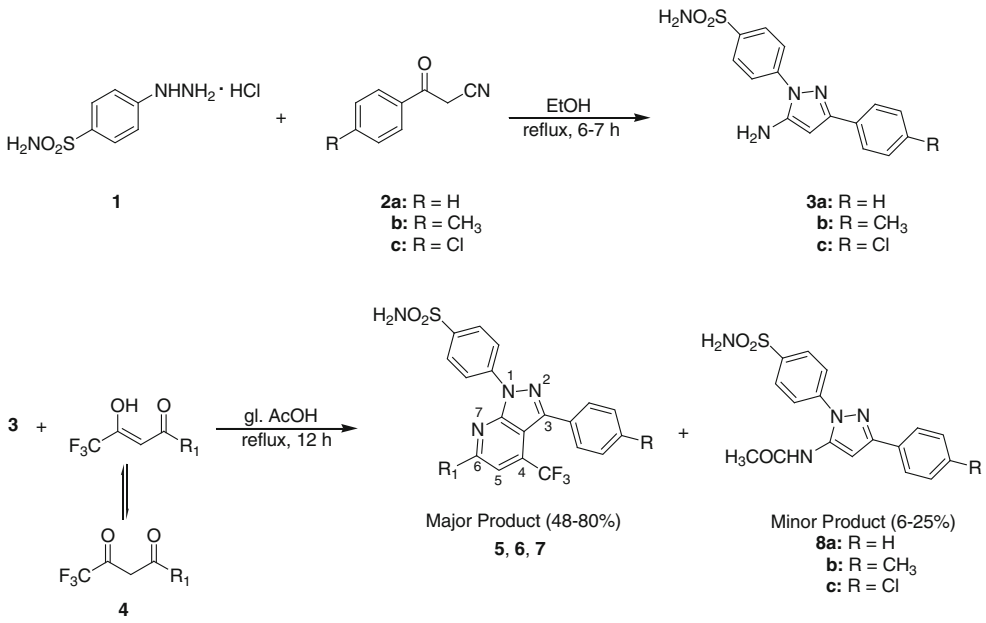
Results and discussion

Chemistry

The synthetic route used to synthesize the target pyrazolo[3,4-*b*]pyridines (**5**–**7**) is outlined in Scheme 1. The starting materials, various α-cyanoacetophenones (**2a**–**c**) were readily prepared by the reaction of appropriate *p*-substituted phenacyl bromides with potassium cyanide in aqueous ethanol at 50 °C following literature procedure (Gakhar *et al.*, 1971). 4-Hydrazinobenzenesulfonamide hydrochloride (**1**) was prepared via diazotization of sulfanilamide followed by reduction of the corresponding diazonium salt with stannous chloride (Soliman, 1979). Reaction of **1** with appropriate α-cyanoacetophenone (**2**) in refluxing ethanol gave corresponding 4-(5-amino-3-aryl-1*H*-pyrazol-1-yl)benzenesulfonamide (**3a**–**c**) following our earlier adapted procedure (Sharma *et al.*, 2011a). The reaction of 5-aminopyrazoles with unsymmetrical 1,3-diketones especially trifluoromethyl-*β*-diketones has been a subject matter of intense investigation in the recent past. Formation of two different regioisomers of pyrazolo[3,4-*b*]pyridine has been reported in the literature, under similar reaction conditions, differing only in the position of CF_3 which can be either at 4-position (Emelina *et al.*, 2008) or at 6-position (Singh *et al.*, 2004b; Sharma *et al.*, 2011a) of the pyrazolopyridine nucleus. ^{19}F NMR spectroscopy has played a decisive role in establishing the structure of the isomeric compound. It is reported in the literature (Numann *et al.*, 1985) that the CF_3 group at *ortho*-position in pyridine displays signal at higher negative value as compared to that of *para*-position in ^{19}F NMR. The relative difference in values at *ortho*- and *para*-positions may be attributed to the presence of nitrogen at adjacent position attached via a double bond. A very recent report (Aggarwal *et al.*, 2012) has shown on the basis of ^{13}C, ^{19}F, and HMBC experiments that solvent mediated stepwise synthesis of pyrazolo[3,4-*b*]pyridine gave single regioisomer with CF_3 at 4-position. Earlier reports presumed that the reaction of 5-aminopyrazoles with trifluoromethyl-*β*-diketones is initiated exclusively by the attack of amino group on the carbonyl carbon adjoining the CF_3 group (Singh *et al.*, 2004b). However, it is now believed that carbonyl carbon adjacent to CF_3 remains in hydrated form in protic solvent, making attack of amino group forcibly on other carbonyl carbon.

As far as the choice of solvent is concerned, the only solvent which has been reported to work fine for pyrazolopyridine formation is glacial acetic acid (Joshi *et al.*, 1979; Singh *et al.*, 2004b; Sharma *et al.*, 2011a) which has been further supported by a recently published paper (Hao *et al.*, 2012). However, in our hands, coupling of **3** with various trifluoromethyl-*β*-diketones **4** in refluxing glacial acetic acid gave two products, one desired isomer pyrazolo[3,4-*b*]pyridines (**5**–**7**) in major amount along with acylated 5-aminopyrazoles (**8a**–**c**) in minor amount. The formation of a side product like **8** in this reaction offers the most probable reason for a moderate to low yield reported in the literature for the synthesis of fused pyrazolopyridines (Joshi *et al.*, 1979; Singh *et al.*, 2004b; Sharma *et al.*, 2011a; Aggarwal *et al.*, 2012). The formation of **8** was conclusively proved by refluxing 5-aminopyrazoles (**3**) in glacial acetic acid in the absence of *β*-diketones where the sole product obtained was acylated 5-aminopyrazoles (**8a**–**c**) in high yield (86–92 %). It reveals that both the reactions, i.e., (i) nucleophilic attack of amino group on the carbonyl carbon, and (ii) amino acylation, go side by side and compete with each other. We observed that substitution of group **R** in 5-aminopyrazole plays an important role for controlling yield ratio of both the products. Amount of acylation follows the substituent order $-CH_3$ (∼10 %) < –H (∼15 %) < –Cl (∼20 %) revealing that acylation is less when **R** group is electron releasing (**3a**, CH_3) in nature

Scheme 1 Synthesis of pyrazolo[3,4-*b*]pyridines (**5**–**7**)



R1 (4) / R (3)	—CH_3	—CF_3	H	CH_3	OCH_3	F	Cl	Br		S
—H	**5a**	**5b**	**5c**	**5d**	**5e**	**5f**	**5g**	**5h**	**5i**	**5j**
—CH_3	**6a**	**6b**	**6c**	**6d**	**6e**	**6f**	**6g**	**6h**	**6i**	**6j**
—Cl	**7a**	**7b**	**7c**	**7d**	**7e**	**7f**	**7g**	**7h**	**7i**	**7j**

and more when **R** is electron withdrawing (**3c**, Cl). Acylated compounds (**8a**–**c**) were easily separated from the desired pyrazolopyridines (**5a**–**j**, **6a**–**j**, and **7a**–**j**) by fractional crystallization from ethanol without using column chromatography because of poor solubility of acylated product in ethanol.

Spectral data (^{1}H NMR, ^{13}C NMR, ^{19}F NMR, IR, and mass) of the newly synthesized compounds were in full agreement with the proposed structures. In general, 5-aminopyrazoles (**3a**–**c**) were characterized by the presence of pyrazole C_4-H proton resonating in the range δ 5.93–5.99 appearing as a singlet and amino group resonating in the narrow range δ 5.65–5.71 appearing as an exchangeable singlet in ^{1}H NMR. Pyrazolo[3,4-*b*]pyridines (**5a**–**j**, **6a**–**j**, and **7a**–**j**) were identified by the presence of a singlet for pyridine C_5-H proton resonating in the range δ 7.75–7.79 in **5a**, **6a**, and **7a**, δ 8.99–9.00 in **5i**, **6i** and **7i** and δ 8.20–8.37 in others, sometimes merging with aromatic protons in ^{1}H NMR. Position of CF_3 (C_4-CF_3) in range δ −58.58 to −59.01 which was in agreement with those reported for similar structures in literature (Numann *et al.*, 1985; Aggarwal *et al.*, 2012). ^{19}F NMR signal of C_6-CF_3 resonates in the narrow range δ −65.45 to −65.47 as in the case of **5b**, **6b**, and **7b**. Acylated 5-aminopyrazoles, **8a**–**c** were characterized by the presence of an exchangeable singlet in the narrow range δ 10.18–10.20 due to NH proton and another singlet at δ 2.03 due to three protons of CH_3 group in ^{1}H NMR.

Antimicrobial evaluation

All the thirty synthesized target compounds (**5a**–**j**, **6a**–**j**, and **7a**–**j**) were assayed for their in vitro antimicrobial activity against *Staphylococcus aureus* (MTCC 96) and *Bacillus subtilis* (MTCC 121) representing Gram-positive bacteria, *Escherichia coli* (MTCC 1652) and *Pseudomonas aeruginosa* (MTCC 741) representing Gram-negative bacteria, and *Saccharomyces cerevisiae* (MTCC 170) and *Candida*

albicans (MTCC 227) representing fungal yeasts (Table 1) by agar well diffusion method (Ahmad and Beg, 2001; Andrews, 2001) using ciprofloxacin against bacteria and amphotericin-B against fungi as the reference drugs. The results were recorded for each tested compound as the average diameter of inhibition zones of microbial growth surrounding the well in mm. The minimum inhibitory concentration (MIC) measurements were performed using a modified agar well diffusion method (Okeke *et al.*, 2001) (Table 2).

Results revealed that in general, all the tested compounds except **7c**–**7h** possessed variable antibacterial activity against both the Gram-positive bacteria (*S. aureus*, *B. subtilis*) and some of the compounds (**5a**–**f**, **5h**, **6i**, **7b**) possessed moderate antifungal activity against both the yeasts (*S. cerevisiae*, *C. albicans*). However, none of them was found to be effective against any Gram-negative bacteria (*E. coli*, *P. aeruginosa*). On the basis of zone of inhibition against the test bacterium, two compounds (**5b** and **5d)** were found to be the most effective against *S. aureus* showing zone of inhibition 22.6

Table 1 In vitro antimicrobial activity of compounds **5**–**7** through agar well-diffusion method

Compounds[a]	Diameter of growth of inhibition zone (mm)[b]					
	Staphylococcus aureus	*Bacillus subtilis*	*Escherichia coli*	*Pseudomonas aeruginosa*	*Saccharomyces cerevisiae*	*Candida albicans*
5a	19.3	20.3	–	–	15.3	16.3
5b	22.6	21.6	–	–	14.6	15.6
5c	18.6	17.0	–	–	16.3	15.3
5d	21.3	20.3	–	–	15.6	16.3
5e	19.3	21.6	–	–	14.6	15.6
5f	17.6	19.6	–	–	15.3	14.6
5g	15.0	16.3	–	–	–	–
5h	18.3	17.6	–	–	14.6	13.6
5i	13.6	14.6	–	–	–	–
5j	14.6	15.6	–	–	–	–
6a	15.3	16.3	–	–	–	–
6b	15.6	16.6	–	–	–	–
6c	18.3	17.6	–	–	–	–
6d	15.3	16.3	–	–	–	–
6e	14.6	17.3	–	–	–	–
6f	13.6	15.6	–	–	–	–
6g	15.6	16.3	–	–	–	–
6h	14.3	15.6	–	–	–	–
6i	15.6	15.6	–	–	15.6	18.3
6j	15.3	16.3	–	–	–	–
7a	18.6	17.6	–	–	–	–
7b	16.3	15.6	–	–	14.6	16.3
7c	–	–	–	–	–	–
7d	–	–	–	–	–	–
7e	–	–	–	–	–	–
7f	–	–	–	–	–	–
7g	–	–	–	–	–	–
7h	–	–	–	–	–	–
7i	15.3	16.3	–	–	–	–
7j	14.6	15.6	–	–	–	–
Ciprofloxacin	26.6	24.0	25.0	22.0	Nt	Nt
Amphotericin-B	Nt	Nt	Nt	Nt	19.3	16.6

–, No activity; Nt, not tested

[a] Concentration 4.0 mg/mL

[b] Values, including diameter of the well (8 mm), are means of three replicates

Table 2 Minimum inhibitory concentration (MIC) (in μg/mL) of compounds **5–7** by using modified agar well-diffusion method

Compound	*Staphylococcus aureus*	*Bacillus subtilis*	*Saccharomyces cerevisiae*	*Candida albicans*
5a	64	64	64	64
5b	32	32	128	64
5c	64	128	64	64
5d	32	64	64	64
5e	64	32	256	128
5f	128	64	64	128
5g	128	128	Nt	Nt
5h	64	64	256	>256
5i	256	256	Nt	Nt
5j	256	128	Nt	Nt
6a	128	128	Nt	Nt
6b	128	128	Nt	Nt
6c	64	128	Nt	Nt
6d	128	128	Nt	Nt
6e	256	128	Nt	Nt
6f	>256	128	Nt	Nt
6g	128	128	Nt	Nt
6h	256	128	Nt	Nt
6i	128	128	32	32
6j	128	128	Nt	Nt
7a	64	128	Nt	Nt
7b	128	128	64	64
7i	128	128	Nt	Nt
7j	128	128	Nt	Nt
Ciprofloxacin	5	5	Nt	Nt
Amphotericin-B	Nt	Nt	20	20

Nt not tested

and 21.3 mm, respectively, while four compounds showing zone of inhibition 21.6 (**5b** and **5e**) and 20.3 mm (**5a** and **5d**) against *B. subtilis* (Table 1) when compared with standard drug ciprofloxacin which showed the zone of inhibition 26.6 mm against *S. aureus* and 24.0 mm against *B. subtilis*. Besides **5b** and **5d**, six compounds (**5a**, **5c**, **5e**, **5h**, **6c**, and **7a**) showed moderate antibacterial activity against *S. aureus* with zone of inhibition >18.0 mm while compound **5f** showed moderate antibacterial activity against *B. subtilis* with zone of inhibition 19.6 mm. Rest of the compounds did not show any significant antibacterial activity against any of the Gram-positive bacteria. However, in terms of MIC, none of the compounds was found to possess appreciable antibacterial activity. Amongst all the active compounds, the MIC ranged between 32 and ≥256 μg/mL against Gram-positive bacteria as compared to standard drug ciprofloxacin having MIC of 5 μg/mL (Table 2). Compound **5b** was found to be the most potent member in the whole series in terms of zone of inhibition as well as MIC.

In case of fungal yeasts, only nine compounds (**5a–f**, **5h**, **6i**, and **7b**) were found to be active. Amongst them, compound **5c** was found to be the most effective against *S. cervisiae* showing zone of inhibition 16.3 mm and four compounds against *C. albicans* producing zone of inhibition 18.3 mm (**6i**) and 16.3 mm (**5a**, **5d**, and **7b**) when compared with standard drug amphotericin-B producing zone of inhibition 19.3 mm against *S. cerevisiae* and 16.6 mm against *C. albicans*. Rest of the compounds showed moderate antifungal activity against *S. cervisiae* as well as *C. albicans* producing zone of inhibition >14.0 and >13.0 mm, respectively (Table 1). However, none of the compounds was found to be close to the standard drug in terms of MIC. Amongst the all active compounds, the MIC ranged between 32 and ≥256 μg/mL against fungal yeasts as compared to standard drug amphotericin-B having MIC of 20 μg/mL (Table 2). Out of all the compounds synthesized, compound **5c** was found to be the most potent against *S. cerevisiae* and **6i** against *C. albicans* in terms of zone of inhibition as well as MIC.

Analysis of the results in terms of structure–activity relationship indicates that in general, pyrazolopyridines **5**, bearing a phenyl group at C-3 of pyrazole, exhibited better

antibacterial as well as antifungal activity as compared to analogues **6** and **7**, bearing a *p*-toluyl and *p*-chlorophenyl group, respectively, in terms of zone of inhibition as well as MIC pointing that the presence of either an electron releasing (**6**) or electron withdrawing **R** group (**7**) results in decrease of both types of activities. No correlation could be drawn within individual homologues of **5**, **6**, and **7** with respect to group $\mathbf{R_1}$.

Conclusion

The objective of this study was to synthesize and investigate antimicrobial activity of a library of novel pyrazolo [3,4-*b*]pyridines bearing benzenesulfonamide and trifluoromethyl moieties with electron releasing or electron withdrawing groups (**R** and $\mathbf{R_1}$). Pyrazolopyridines **5** having a phenyl substituent were found to exhibit better antimicrobial activity as compared to analogues **6** and **7**. Out of the tested compounds, **5b** was found to be the most potent analogue exhibiting moderate antibacterial activity against Gram-positive bacteria while **5c** and **6i** exhibiting moderate antifungal activity against *S. cerevisiae* and *C. albicans*, respectively. However, none of the newly synthesized compounds was found to be superior over the reference drugs.

Experimental protocols

All reactions were carried out under atmospheric pressure. Melting points were determined in open glass capillaries in an electrical melting point apparatus and are uncorrected. The infrared (IR) spectra were recorded on ABB MB 3000 DTGS FT-IR Spectrophotometer using the KBr pellet technique. ^{1}H NMR and ^{13}C NMR spectra were recorded either in pure DMSO-d_6 or in $CDCl_3$/DMSO-d_6 mixture on Bruker NMR spectrometers at 300/400 and 75.5/100 MHz, respectively, using tetramethylsilane (TMS) as internal standard, whereas ^{19}F NMR spectra were recorded at 376.4 MHz in DMSO-d_6 using fluorinated chloromethane, $CFCl_3$ as an internal standard. Chemical shifts are expressed in δ, ppm. Mass spectra (DART-MS) were recorded on a JEOL-AccuTOF JMS-T100LC Mass spectrometer having a DART (direct analysis in real time) source in ES^+ mode. The purity of the compounds was checked by ^{1}H NMR and thin layer chromatography (TLC) on silica gel plates using a mixture of petroleum ether and ethyl acetate as eluent. Iodine or UV lamp was used as a visualizing agent. Abbreviations "s" for singlet, "d" for doublet, "m" for multiplet, "ex" for exchangeable proton are used for NMR assignments and "s" for strong, "m" for medium for IR assignments. "d" stands for decomposition in melting point data. Trifluoromethyl-β-diketones, **4a–c** and **4j** were purchased from ACROS-ORGANICS, New Jersey, USA and remaining diketones (Singh *et al.*, 2004a; Sloop *et al.*, 2006; Ahlström *et al.*, 2007) as well as α-cynaoacetophenones (**2a–c**) (Gakhar *et al.*, 1971) were prepared using established literature procedures and confirmed by their available spectral data and melting points.

General procedure for the preparation of 5-aminopyrazoles (**3a–c**)

Appropriate α-cyanoacetophenone (**2**, 24 mmol) was dissolved in ethanol (100 mL) by warming at 50 °C followed by the addition of 4-hydrazinobenzenesulfonamide hydrochloride (**1**, 20 mmol) along with four to five drops of acetic acid and the reaction mixture was refluxed for 5–6 h. After completion of the reaction, solution was reduced to 1/3rd of its volume and cooled to room temperature. Crystalline solid separated out which was filtered, washed with water (100 mL) followed by cold ethanol (20 mL), dried and recrystallized from aqueous ethanol to afford target 5-aminopyrazoles **3**.

*4-(5-Amino-3-phenyl-1H-pyrazol-1-yl)benzenesulfonamide (**3a**)*

Yield: 64 %; m.p. 183–185 °C (Sharma *et al.* 2011a); IR (KBr) cm^{-1}: 3356, 3302 and 3263 (m, N–H stretch), 1628 (s, C=N stretch), 1597 (s, C=N stretch), 1512 (m, N–H bend), 1327 and 1165 (s, SO_2 stretch); ^{1}H NMR (300 MHz, DMSO-d_6): δ 7.88–7.95 (m, 4H, Ar), 7.78 (d, 2H, $J = 7.2$ Hz, Ar), 7.43 (s, ex, 2H, SO_2NH_2), 7.40 (d, 2H, $J = 7.2$ Hz, Ar), 7.32 (t, 1H, $J = 7.2$ Hz, Ar), 5.97 (s, 1H, pyrazole C_4-H), 5.68 (s, ex, 2H, NH_2); ^{13}C NMR (75.5 MHz, DMSO-d_6): δ 151.4, 149.3, 142.3, 141.6, 133.6, 129.0, 128.3, 127.3, 125.6, 123.5, 122.7, 88.6.

*4-[5-Amino-3-(4-methylphenyl)-1H-pyrazol-1-yl]benzenesulfonamide (**3b**)*

Yield 70 %; m.p. 242–244 °C; IR (KBr) cm^{-1}: 3356, 3302, and 3263 (m, N–H stretch), 1628 (s, C=N stretch), 1597 (s, C=N stretch), 1512 (m, N–H bend), 1327 and 1165 (s, SO_2 stretch); ^{1}H NMR (300 MHz, DMSO-d_6): δ 7.93 (d, 2H, $J = 9.0$ Hz, Ar), 7.90 (d, 2H, $J = 9.0$ Hz, Ar), 7.67 (d, 2H, $J = 8.1$ Hz, Ar), 7.44 (s, ex, 2H, SO_2NH_2), 7.21 (d, 2H, $J = 8.1$ Hz, Ar), 5.93 (s, 1H, pyrazole C_4-H), 5.65 (s, ex, 2H, NH_2), 2.32 (CH_3); ^{13}C NMR (75.5 MHz, DMSO-d_6): δ 151.4, 149.2, 142.3, 141.4, 137.6, 130.9, 129.5, 127.2, 125.6, 122.5, 88.4, 21.3 (CH_3).

*4-[5-Amino-3-(4-chlorophenyl)-1H-pyrazol-1-yl]benzenesulfonamide (**3c**)*

Yield 65 %; m.p. 220–221 °C; IR (KBr) cm^{-1}: 3371, 3271 & 3202 (m, N–H stretch), 1628 (s, C=N stretch), 1597 (s,

C=N stretch), 1512 (m, N–H bend), 1327 and 1157 (s, SO_2 stretch); ^{1}H NMR (300 MHz, DMSO-d_6): δ 7.95 (d, 2H, J = 9.0 Hz, Ar), 7.90 (d, 2H, J = 9.0 Hz, Ar), 7.81 (d, 2H, J = 8.4 Hz, Ar), 7.45–7.47 (m, 4H, SO_2NH_2, Ar), 5.99 (s, 1H, pyrazole C_4-H), 5.71 (s, ex, 2H, NH_2); ^{13}C NMR (75.5 MHz, DMSO-d_6): δ 150.2, 149.5, 142.2, 141.7, 132.7, 132.5, 129.0, 127.3, 127.2, 124.9, 122.7, 88.4.

General procedure for the preparation of pyrazolo[3,4-*b*]pyridines (**5a**–**j**, **6a**–**j**, and **7a**–**j**)

A solution of appropriate 5-aminopyrazole (**3**, 1.5 mmol) and appropriate trifluoromethyl-β-diketone (**4**, 1.8 mmol) in glacial acetic acid (8 mL) was refluxed for 10–12 h. After completion of the reaction, the contents were poured into ice cold water and stirred vigorously whereupon solid separated out which was filtered, washed with excess of cold water and dried to afford a crude mixture which upon fractional crystallization from ethanol yielded two products: pyrazolo[3,4-*b*]pyridines (**5**, **6**, or **7**) in major amount and 5-acetamidopyrazoles (**8a**–**c**) in minor amount.

*4-[6-Methyl-3-phenyl-4-(trifluoromethyl)-1H-pyrazolo[3,4-b]pyridin-1-yl]benzenesulfonamide (**5a**)*

Yield 60 %; m.p. 248–250 °C; IR (KBr) cm^{-1}: 3348 & 3240 (m, N–H stretch), 1597 (s, C=N stretch), 1504 (m, N–H bend), 1335 and 1149 (s, SO_2 stretch); ^{1}H NMR (300 MHz, DMSO-d_6): δ 8.49 (d, 2H, J = 8.7 Hz, Ar), 8.04 (d, 2H, J = 8.7 Hz, Ar), 7.75 (s, 1H, pyridine C_5-H), 7.51–7.55 (m, 5H, Ar), 7.48 (s, ex, 2H, SO_2NH_2), 2.80 (s, 3H, CH_3); ^{13}C NMR (75.5 MHz, DMSO-d_6): δ 161.2, 151.6, 145.6, 142.1, 141.2, 132.9 131.3, 130.8, 130.0, 129.5, 128.4, 127.4, 124.5, 121.7, 120.9, 116.7, 116.6, 108.8, 25.1 (CH_3); ^{19}F NMR (376.4 MHz, DMSO-d_6): δ –59.01 (C_4-CF_3); DART-MS: *m/z* 433.12 $(M+H)^+$, $C_{20}H_{15}F_3N_4O_2SH^+$ calcd. 433.08.

*N-{1-[4-(Aminosulfonyl)phenyl]-3-phenyl-1H-pyrazol-5-yl}acetamide (**8a**)*

Yield 13 %; m.p. 254–256 °C; IR (KBr) cm^{-1}: 3271 (m, N–H stretch), 1666 (s, C=O stretch), 1597 (s, C=N stretch), 1327 and 1157 (s, SO_2 stretch); ^{1}H NMR (300 MHz, DMSO-d_6): δ 10.19 (s, ex, 1H, NHCO), 7.96 (d, 2H, J = 8.4 Hz, Ar), 7.87 (d, 2H, J = 8.1 Hz, Ar), 7.80 (d, 2H, J = 8.4 Hz, Ar), 7.47 (s, ex, 2H, SO_2NH_2), 7.40–7.42 (m, 3H, Ar), 6.92 (s, 1H, pyrazole C_4-H), 2.03 (s, 3H, NHCO*CH*$_3$); ^{13}C NMR (75.5 MHz, DMSO-d_6): δ 169.5 (NHCO), 151.3, 142.9, 141.5, 138.2, 132.9, 129.2, 128.7, 127.3, 125.7, 123.8, 100.8, 23.3 (NHCO*CH*$_3$).

*4-[3-Phenyl-4,6-bis(trifluoromethyl)-1H-pyrazolo[3,4-b]pyridin-1-yl]benzenesulfonamide (**5b**)*

Yield 71 %; m.p. 240–242 °C (Sharma *et al.*, 2011a); IR (KBr) cm^{-1}: 3356 and 3271 (m, N–H stretch), 1597 (s, C=N stretch), 1504 (m, N–H bend), 1335 and 1142 (s, SO_2 stretch); ^{1}H NMR (300 MHz, DMSO-d_6): δ 8.41 (d, 2H, J = 8.7 Hz, Ar), 8.27 (s, 1H, pyridine C_5-H), 8.09 (d, 2H, J = 8.7 Hz, Ar), 7.56-7.64 (m, 5H, Ar), 7.51 (s, ex, 2H, SO_2NH_2); ^{13}C NMR (75.5 MHz, DMSO-d_6): δ 150.5, 146.9, 146.5, 146.0, 143.0, 140.4, 133.4, 132.1, 130.1, 129.9, 128.5, 127.6, 122.3, 113.5, 112.5; ^{19}F NMR (376.4 MHz, DMSO-d_6): δ –58.64 (C_4-CF_3), –65.46 (C_6-CF_3); DART-MS: *m/z* 487.10 $(M+H)^+$, $C_{20}H_{12}F_6N_4O_2SH^+$ calcd. 487.05.

(**8a**) Yield 11 %.

*4-[3,6-Diphenyl-4-(trifluoromethyl)-1H-pyrazolo[3,4-b]pyridin-1-yl]benzenesulfonamide (**5c**)*

Yield 58 %; m.p. 234–236 °C; IR (KBr) cm^{-1}: 3286 and 3217 (m, N–H stretch), 1597 (s, C=N stretch), 1504 (m, N–H bend), 1335 and 1157 (s, SO_2 stretch); ^{1}H NMR (300 MHz, DMSO-d_6): δ 8.57 (d, 2H, J = 8.7 Hz, Ar), 8.34–8.38 (m, 3H, pyridine C_5-H, Ar), 8.10 (d, 2H, J = 8.7 Hz, Ar), 7.56–7.63 (m, 4H, Ar), 7.45–7.50 (m, 4H, SO_2NH_2, Ar), 7.40–7.41 (m, 2H, Ar); ^{13}C NMR (75.5 MHz, DMSO-d_6): δ 157.7, 151.3, 145.8, 142.2, 141.1, 137.1, 131.3, 130.0, 129.6, 128.4, 128.2, 127.5, 121.8, 114.4, 109.2; ^{19}F NMR (376.4 MHz, DMSO-d_6): δ –58.75 (C_4-CF_3); DART-MS: *m/z* 495.15 $(M+H)^+$, $C_{25}H_{17}F_3N_4O_2SH^+$ calcd. 495.10.

(**8a**) Yield 17 %.

*4-[6-(4-Methylphenyl)-3-phenyl-4-(trifluoromethyl)-1H-pyrazolo[3,4-b]pyridin-1-yl]benzenesulfonamide (**5d**)*

Yield 59 %; m.p. 260–262 °C; IR (KBr) cm^{-1}: 3340 & 3232 (m, N–H stretch), 1597 (s, C=N stretch), 1497 (m, N–H bend), 1358 and 1142 (s, SO_2 stretch); ^{1}H NMR (300 MHz, DMSO-d_6): δ 8.57 (d, 2H, J = 8.7 Hz, Ar), 8.28-8.30 (m, 3H, pyridine C_5-H, Ar), 8.10 (d, 2H, J = 8.7 Hz, Ar), 7.54–7.62 (m, 5H, Ar), 7.48 (s, ex, 2H, SO_2NH_2), 7.43 (d, 2H, J = 8.1 Hz, Ar), 2.42 (s, 3H, CH_3); ^{13}C NMR (75.5 MHz, DMSO-d_6): δ 157.7, 151.8, 145.8, 142.1, 141.3, 141.1, 134.4, 132.8, 130.2, 130.0, 129.5, 128.4, 128.1, 127.5, 121.7, 115.0, 112.8, 109.1, 21.4 (CH_3); ^{19}F NMR (376.4 MHz, DMSO-d_6): δ –58.75 (C_4-CF_3); DART-MS: *m/z* 509.20 $(M+H)^+$, $C_{26}H_{19}F_3N_4O_2SH^+$ calcd. 509.11.

(**8a**) Yield 15 %.

*4-[6-(4-Methoxyphenyl)-3-phenyl-4-(trifluoromethyl)-1H-pyrazolo[3,4-b]pyridin-1-yl]benzenesulfonamide (**5e**)*

Yield 59 %; m.p. 270–271 °C; IR (KBr) cm^{-1}: 3302 & 3240 (m, N–H stretch), 1597 (s, C=N stretch), 1512 (m, N–H bend), 1358 and 1142 (s, SO_2 stretch); ^1H NMR (300 MHz, DMSO-d_6): δ 8.57 (d, 2H, $J = 8.7$ Hz, Ar), 8.36 (d, 2H, $J = 8.4$ Hz, Ar), 8.26 (s, 1H, pyridine C_5-H), 8.10 (d, 2H, $J = 8.4$ Hz, Ar), 7.49–7.60 (m, 7H, SO_2NH_2, Ar), 7.15 (d, 2H, $J = 8.7$ Hz, Ar), 3.87 (s, 3H, OCH_3); ^{13}C NMR (75.5 MHz, DMSO-d_6): δ 162.0, 157.3, 151.8, 145.8, 142.1, 141.2, 132.9, 131.8, 130.0, 129.8, 129.5, 128.4, 127.5, 121.6, 115.0, 112.7, 109.1, 55.8 (OCH_3); ^{19}F NMR (376.4 MHz, DMSO-d_6): δ –58.85 (C_4-CF_3); DART-MS: *m/z* 525.19 $(M+H)^+$, $C_{26}H_{19}F_3N_4O_3SH^+$ calcd. 525.11.

(**8a**) Yield 15 %.

*4-[6-(4-Fluorophenyl)-3-phenyl-4-(trifluoromethyl)-1H-pyrazolo[3,4-b]pyridin-1-yl]benzenesulfonamide (**5f**)*

Yield 57 %; m.p. 230–232 °C; IR (KBr) cm^{-1}: 3302 and 3271 (m, N–H stretch), 1597 (s, C=N stretch), 1504 (m, N–H bend), 1342 and 1149 (s, SO_2 stretch); ^1H NMR (300 MHz, DMSO-d_6): δ 8.55 (d, 2H, $J = 8.7$ Hz, Ar), 8.46 (dd, 2H, $^4J_{HF} = 5.4$ Hz, $^3J_{HH} = 8.4$ Hz, Ar), 8.33 (s, 1H, pyridine C_5-H), 8.09 (d, 2H, $J = 8.7$ Hz, Ar), 7.54–7.56 (m, 3H, Ar), 7.49 (s, 4H, SO_2NH_2, Ar), 7.44 (t, 2H, $J = 8.7$ Hz, Ar); ^{13}C NMR (100 MHz, $CDCl_3$/DMSO-d_6): δ 156.1, 151.3, 145.3, 141.3, 140.8, 137.4, 133.1, 132.3, 132.1, 129.69, 129.60, 126.8, 126.7, 125.0, 123.1, 120.7, 115.9, 115.7; ^{19}F NMR (376.4 MHz, DMSO-d_6): δ –58.70 (C_4-CF_3); DART-MS: *m/z* 513.15 $(M+H)^+$, $C_{25}H_{16}F_4N_4O_2SH^+$ calcd. 513.09.

(**8a**) Yield 17 %.

*4-[6-(4-Chlorophenyl)-3-phenyl-4-(trifluoromethyl)-1H-pyrazolo[3,4-b]pyridin-1-yl]benzenesulfonamide (**5g**)*

Yield 60 %; m.p. 287–288 °C; IR (KBr) cm^{-1}: 3379 and 3279 (m, N–H stretch), 1589 (s, C=N stretch), 1497 (m, N–H bend), 1342 and 1134 (s, SO_2 stretch); ^1H NMR (300 MHz, DMSO-d_6): δ 8.55 (d, 2H, $J = 8.7$ Hz, Ar), 8.42 (d, 2H, $J = 8.4$ Hz, Ar), 8.35 (s, 1H, pyridine C_5-H), 8.09 (d, 2H, $J = 8.7$ Hz, Ar), 7.67 (d, 2H, $J = 8.7$ Hz, Ar), 7.61–7.63 (m, 2H, Ar), 7.55–7.56 (m, 3H, Ar), 7.50 (s, ex, 2H, SO_2NH_2); ^{13}C NMR (75.5 MHz, DMSO-d_6): δ 156.4, 151.7, 145.8, 142.2, 141.0, 136.2, 135.9, 132.7, 132.6, 130.0, 129.6, 128.4, 127.6, 125.0, 121.8, 113.3, 109.9; ^{19}F NMR (376.4 MHz, DMSO-d_6): δ –58.76 (C_4-CF_3); DART-MS: *m/z* 529.11 $(M+H)^+$, $C_{25}H_{16}ClF_3N_4O_2SH^+$ calcd. 529.06.

(**8a**) Yield 13 %.

*4-[6-(4-Bromophenyl)-3-phenyl-4-(trifluoromethyl)-1H-pyrazolo[3,4-b]pyridin-1-yl]benzenesulfonamide (**5h**)*

Yield 62 %; m.p. 278–280 °C; IR (KBr) cm^{-1}: 3379 and 3286 (m, N–H stretch), 1589 (s, C=N stretch), 1504 (m, N–H bend), 1342 and 1134 (s, SO_2 stretch); ^1H NMR (300 MHz, DMSO-d_6): δ 8.55 (d, 2H, $J = 8.7$ Hz, Ar), 8.32–8.34 (m, 3H, pyridine C_5-H, Ar), 8.09 (d, 2H, $J = 8.7$ Hz, Ar), 7.80 (d, 2H, $J = 8.7$ Hz, Ar), 7.56–7.60 (m, 5H, Ar), 7.50 (s, ex, 2H, SO_2NH_2); ^{13}C NMR (75.5 MHz, DMSO-d_6): δ 156.5, 151.7, 145.8, 142.2, 141.0, 136.3, 132.7, 132.5, 130.2, 130.0, 129.6, 128.4, 127.6, 125.1, 113.4, 110.0; ^{19}F NMR (376.4 MHz, DMSO-d_6): δ −58.77 (C_4-CF_3); DART-MS: *m/z* 573.10 $(M+H)^+$, $C_{25}H_{16}BrF_3N_4O_2SH^+$ calcd. 573.01.

(**8a**) Yield 13 %.

*4-[6-(2-Naphthyl)-3-phenyl-4-(trifluoromethyl)-1H-pyrazolo[3,4-b]pyridin-1-yl]benzenesulfonamide (**5i**)*

Yield 55 %; m.p. 278–280 °C; IR (KBr) cm^{-1}: 3371 and 3286 (m, N–H stretch), 1597 (s, C=N stretch), 1504 (m, N–H bend), 1342 and 1126 (s, SO_2 stretch); ^1H NMR (300 MHz, DMSO-d_6): δ 9.00 (s, 1H, pyridine C_5-H), 8.62 (d, 2H, $J = 8.7$ Hz, Ar), 8.50–8.53 (m, 2H, Ar), 8.12–8.18 (m, 4H, Ar), 8.00–8.03 (m, 1H, Ar), 7.61–7.64 (m, 4H, Ar), 7.56–7.57 (m, 3H, Ar), 7.50 (s, ex, 2H, SO_2NH_2); ^{13}C NMR (75.5 MHz, DMSO-d_6): δ 157.5, 151.8, 145.9, 142.2, 141.1, 134.4, 134.3, 133.4, 132.8, 130.0, 129.6, 129.5, 129.2, 128.6, 128.4, 128.1, 128.0, 127.6, 127.2, 124.9, 121.8, 114.4, 109.7; ^{19}F NMR (376.4 MHz, DMSO-d_6): δ −58.73 (C_4-CF_3); DART-MS: *m/z* 545.16 $(M+H)^+$, $C_{29}H_{19}F_3N_4O_2SH^+$ calcd. 545.11.

(**8a**) Yield 17 %.

*4-[3-Phenyl)-4-(2-thienyl)-6-(trifluoromethyl)-1H-pyrazolo[3,4-b]pyridin-1-yl]benzenesulfonamide (**5j**)*

Yield 57 %; m.p. 288–290 °C; IR (KBr) cm^{-1}: 3371 and 3271 (m, N–H stretch), 1597 (s, C=N stretch), 1504 (m, N–H bend), 1366 and 1134 (s, SO_2 stretch); ^1H NMR (300 MHz, DMSO-d_6): δ 8.52 (d, 2H, $J = 8.7$ Hz, Ar), 8.28–8.29 (m, 2H, pyridine C_5-H, thienyl), 8.07 (d, 2H, $J = 8.7$ Hz, Ar), 7.87 (d, 1H, $J = 5.1$ Hz, thienyl), 7.51–7.61 (m, 5H, Ar), 7.49 (s, ex, 2H, SO_2NH_2), 7.28 (t, 1H, $J = 4.5$ Hz, thienyl); ^{13}C NMR (100 MHz, DMSO-d_6): δ 153.0, 151.3, 146.0, 142.9, 142.1, 141.1, 132.7, 131.9, 130.0, 129.6, 128.4, 127.4, 124.4, 121.4, 112.2, 109.4; ^{19}F NMR (376.4 MHz, DMSO-d_6): δ –58.84 (C_4-CF_3); DART-MS: *m/z* 501.15 $(M+H)^+$, $C_{23}H_{15}F_3N_4O_2S_2H^+$ calcd. 501.05.

(**8a**) Yield 14 %.

*4-[6-Methyl-3-(4-methylphenyl)-4-(trifluoromethyl)-1H-pyrazolo[3,4-b]pyridin-1-yl]benzenesulfonamide (**6a**)*

Yield 73 %; m.p. 244–246 °C; IR (KBr) cm^{-1}: 3348 and 3263 (m, N–H stretch), 1597 (s, C=N stretch), 1504 (m, N–H bend), 1319 and 1149 (s, SO_2 stretch); ^1H NMR (300 MHz, DMSO-d_6): δ 8.48 (d, 2H, $J = 8.7$ Hz, Ar), 8.03 (d, 2H, $J = 8.7$ Hz, Ar), 7.75 (s, 1H, pyridine C_5-H), 7.45–7.47 (m, 4H, SO_2NH_2, Ar), 7.33 (d, 2H, $J = 7.8$ Hz, Ar), 2.80 (s, 3H, CH_3), 2.41 (s, 3H, CH_3); ^{13}C NMR (75.5 MHz, DMSO-d_6): δ 161.1, 151.6, 145.7, 142.1, 141.2, 138.9, 131.2, 130.8, 129.9, 129.0, 127.4, 121.7, 116.8, 108.9, 25.1 (CH_3), 21.4 (CH_3); ^{19}F NMR (376.4 MHz, DMSO-d_6): δ –58.94 (C_4-CF_3); DART-MS: *m/z* 447.16 $(M + H)^+$, $C_{21}H_{17}F_3N_4O_2SH^+$ calcd. 447.10.

*N-[1-[4-(Aminosulfonyl)phenyl]-3-(4-methylphenyl)-1H-pyrazol-5-yl]acetamide (**8b**)*

Yield 8 %; m.p. 214–216 °C (d); IR (KBr) cm^{-1}: 3271 (m, N–H stretch), 1666 (s, C=O stretch), 1597 (s, C=N stretch), 1327 and 1157 (s, SO_2 stretch); ^1H NMR (300 MHz, DMSO-d_6): δ 10.18 (s, ex, 1H, NHCO), 7.95 (d, 2H, $J = 8.1$ Hz, Ar), 7.79 (d, 2H, $J = 8.1$ Hz, Ar), 7.75 (d, 2H, $J = 7.8$ Hz, Ar), 7.48 (s, ex, 2H, SO_2NH_2), 7.24 (d, 2H, $J = 7.8$ Hz, Ar), 6.87 (s, 1H, pyrazole C_4-H), 2.33 (s, 3H, CH_3), 2.03 (s, 3H, NHCO*CH_3*); ^{13}C NMR (75.5 MHz, DMSO-d_6): δ 169.5 (NHCO), 151.4, 142.8, 141.6, 138.1, 130.9, 129.8, 127.3, 123.7, 100.7, 23.3 (NHCO*CH_3*), 21.3 (CH_3).

*4-[3-(4-Methylphenyl-4,6-bis(trifluoromethyl)-1H-pyrazolo[3,4-b]pyridin-1-yl]benzenesulfonamide (**6b**)*

Yield 80 %; m.p. 234–236 °C; IR (KBr) cm^{-1}: 3356 and 3263 (m, N–H stretch), 1597 (s, C=N stretch), 1504 (m, N–H bend), 1327 and 1165 (s, SO_2 stretch); ^1H NMR (400 MHz, DMSO-d_6): δ 8.40 (d, 2H, $J = 8.4$ Hz, Ar), 8.22 (s, 1H, pyridine C_5-H), 8.08 (d, 2H, $J = 8.4$ Hz, Ar), 7.49–7.51 (m, 4H, SO_2NH_2, Ar), 7.35 (d, 2H, $J = 7.6$ Hz, Ar), 2.42 (s, 3H, CH_3); ^{13}C NMR (100 MHz, DMSO-d_6): δ 150.0, 146.3, 146.0, 145.5, 142.4, 139.9, 138.9, 133.3, 132.9, 129.4, 128.7, 128.6, 127.1, 122.2, 121.7, 113.1, 112.0, 20.9 (CH_3); ^{19}F NMR (376.4 MHz, DMSO-d_6): δ –58.58 (C_4-CF_3), –65.47 (C_6-CF_3); DART-MS: *m/z* 501.11 $(M+H)^+$, $C_{21}H_{14}F_6N_4O_2SH^+$ calcd. 501.07.

(**8b**) Yield 6 %.

*4-[3-(4-Methylphenyl)-6-phenyl-4-(trifluoromethyl)-1H-pyrazolo[3,4-b]pyridin-1-yl]benzenesulfonamide (**6c**)*

Yield 67 %; m.p. 256–258 °C; IR (KBr) cm^{-1}: 3348 and 3263 (m, N–H stretch), 1597 (s, C=N stretch), 1497 (m, N–H bend), 1327 and 1134 (s, SO_2 stretch); ^1H NMR (300 MHz, DMSO-d_6): δ 8.56 (d, 2H, $J = 8.7$ Hz, Ar), 8.34–8.37 (m, 2H, Ar), 8.29 (s, 1H, pyridine C_5-H), 8.10 (d, 2H, $J = 8.7$ Hz, Ar), 7.59–7.62 (m, 3H, Ar), 7.49–7.51 (m, 4H, SO_2NH_2, Ar), 7.34 (d, 2H, $J = 8.1$ Hz, Ar), 2.42 (s, 3H, CH_3); ^{13}C NMR (75.5 MHz, DMSO-d_6): δ 157.6, 151.8, 145.9, 142.1, 141.1, 139.0, 137.1, 132.0, 131.2, 129.9, 129.6, 129.0, 128.2, 127.5, 121.8, 113.3, 109.8, 21.4 (CH_3); ^{19}F NMR (376.4 MHz, DMSO-d_6): δ –58.73 (C_4-CF_3); DART-MS: *m/z* 509.19 $(M+H)^+$, $C_{26}H_{19}F_3N_4O_2SH^+$ calcd. 509.11.

(**8b**) Yield 10 %.

*4-[3,6-bis(4-Methylphenyl)-4-(trifluoromethyl)-1H-pyrazolo[3,4-b]pyridin-1-yl]benzenesulfonamide (**6d**)*

Yield 62 %; m.p. 250–252 °C; IR (KBr) cm^{-1}: 3340 and 3232 (m, N–H stretch), 1597 (s, C=N stretch), 1497 (m, N–H bend), 1358 & 1142 (s, SO_2 stretch); ^1H NMR (300 MHz, DMSO-d_6): δ 8.56 (d, 2H, $J = 8.7$ Hz, Ar), 8.26–8.29 (m, 3H, pyridine C_5-H, Ar), 8.09 (d, 2H, $J = 8.7$ Hz, Ar), 7.50 (d, 4H, $J = 8.4$ Hz, SO_2NH_2, Ar), 7.41 (d, 2H, $J = 8.1$ Hz, Ar), 7.35 (d, 2H, $J = 7.8$ Hz, Ar), 2.43 (s, 3H, CH_3), 2.42 (s, 3H, CH_3); ^{13}C NMR (75.5 MHz, DMSO-d_6): δ 157.6, 151.8, 145.9, 142.1, 141.3, 141.2, 138.9, 134.4, 130.2, 129.9, 129.0, 128.1, 127.5, 121.7, 113.1, 109.2, 21.4 (CH_3); ^{19}F NMR (376.4 MHz, DMSO-d_6): δ –58.76 (C_4-CF_3); DART-MS: *m/z* 523.21 $(M+H)^+$, $C_{27}H_{21}F_3N_4O_2SH^+$ calcd. 523.13.

(**8b**) Yield 12 %.

*4-[6-(4-Methoxyphenyl)-3-(4-methylphenyl)-4-(trifluoromethyl)-1H-pyrazolo[3,4-b]pyridin-1-yl]benzenesulfonamide (**6e**)*

Yield 59 %; m.p. 274–276 °C; IR (KBr) cm^{-1}: 3348 and 3263 (m, N–H stretch), 1597 (s, C=N stretch), 1504 (m, N–H bend), 1366 and 1149 (s, SO_2 stretch); ^1H NMR (400 MHz, DMSO-d_6): δ 8.56 (d, 2H, $J = 8.8$ Hz, Ar), 8.35 (d, 2H, $J = 8.8$ Hz, Ar), 8.24 (s, 1H, pyridine C_5-H), 8.09 (d, 2H, $J = 8.4$ Hz, Ar), 7.50 (d, 2H, $J = 8.0$ Hz, Ar), 7.48 (s, ex, 2H, SO_2NH_2), 7.34 (d, 2H, $J = 8.0$ Hz, Ar), 7.14 (d, 2H, $J = 9.2$ Hz, Ar), 3.87 (s, 3H, OCH_3), 2.43 (s, 3H, CH_3); ^{13}C NMR (100 MHz, DMSO-d_6): δ 161.5, 156.9, 156.8, 151.4, 145.4, 141.5, 140.7, 138.4, 133.9, 129.5, 129.4, 129.0, 128.5, 127.0, 121.2, 114.5, 112.2, 108.6, 104.1, 55.4 (OCH_3), 20.9 (CH_3); ^{19}F NMR (376.4 MHz, DMSO-d_6): δ –58.78 (C_4-CF_3); DART-MS: *m/z* 539.15 $(M + H)^+$, $C_{27}H_{21}F_3N_4O_3SH^+$ calcd. 539.12.

(**8b**) Yield 12 %.

*4-[6-(4-Fluorophenyl)-3-(4-methylphenyl)-4-(trifluoromethyl)-1H-pyrazolo[3,4-b]pyridin-1-yl]benzenesulfonamide (**6f**)*

Yield 60 %; m.p. 214–216 °C; IR (KBr) cm^{-1}: 3302 and 3248 (m, N–H stretch), 1597 (s, C=N stretch), 1512 (m, N–H bend), 1358 and 1173 (s, SO_2 stretch); ^1H NMR (300 MHz, DMSO-d_6): δ 8.55 (d, 2H, $J = 8.7$ Hz, Ar), 8.44–8.47 (m, 2H, Ar), 8.32 (s, 1H, pyridine C_5-H), 8.09 (d, 2H, $J = 8.7$ Hz, Ar), 7.50 (d, 4H, $J = 7.5$ Hz, SO_2NH_2, Ar), 7.42 (d, 2H, $J = 8.7$ Hz, Ar), 7.35 (d, 2H, $J = 7.5$ Hz, Ar), 2.43 (s, 3H, CH_3); ^{13}C NMR (75.5 MHz, DMSO-d_6): δ 156.6, 151.9, 145.9, 142.2, 141.1, 139.0, 136.3, 134.0, 130.8, 130.7, 129.9, 129.0, 127.6, 121.9, 116.7, 113.3, 21.4 (CH_3); ^{19}F NMR (376.4 MHz, DMSO-d_6): δ –58.71 (C_4-CF_3); DART-MS: *m/z* 527.19 $(M+H)^+$, $C_{26}H_{18}F_4N_4O_2SH^+$ calcd. 527.10.

(**8b**) Yield 10 %.

*4-[6-(4-Chlorophenyl)-3-(4-methylphenyl)-4-(trifluoromethyl)-1H-pyrazolo[3,4-b]pyridin-1-yl]benzenesulfonamide (**6g**)*

Yield 60 %; m.p. 240–242 °C; IR (KBr) cm^{-1}: 3333 and 3240 (m, N–H stretch), 1597 (s, C=N stretch), 1497 (m, N–H bend), 1358 and 1149 (s, SO_2 stretch); ^1H NMR (300 MHz, DMSO-d_6): δ 8.54 (d, 2H, $J = 8.7$ Hz, Ar), 8.40 (d, 2H, $J = 8.4$ Hz, Ar), 8.32 (s, 1H, pyridine C_5-H), 8.09 (d, 2H, $J = 8.7$ Hz, Ar), 7.65 (d, 2H, $J = 8.4$ Hz, Ar), 7.48-7.50 (m, 4H, SO_2NH_2, Ar), 7.34 (d, 2H, $J = 8.1$ Hz, Ar), 2.42 (s, 3H, CH_3); ^{13}C NMR (75.5 MHz, DMSO-d_6): δ 156.3, 151.7, 145.9, 142.1, 141.0, 139.0, 136.2, 135.9, 130.0, 129.9, 129.6, 129.0, 127.5, 121.8, 113.6, 109.9, 21.4 (CH_3); ^{19}F NMR (376.4 MHz, DMSO-d_6): δ –58.70 (C_4-CF_3); DART-MS: *m/z* 543.16 $(M + H)^+$, $C_{26}H_{18}ClF_3N_4O_2SH^+$ calcd. 543.07.

(**8b**) Yield 12 %.

*4-[6-(4-Bromophenyl)-3-(4-methylphenyl)-4-(trifluoromethyl)-1H-pyrazolo[3,4-b]pyridin-1-yl]benzenesulfonamide (**6h**)*

Yield 59 %; m.p. 259–261 °C; IR (KBr) cm^{-1}: 3387 and 3294 (m, N–H stretch), 1589 (s, C=N stretch), 1497 (m, N–H bend), 1350 and 1157 (s, SO_2 stretch); ^1H NMR (400 MHz, DMSO-d_6): δ 8.53 (d, 2H, $J = 8.4$ Hz, Ar), 8.28 (d, 3H, $J = 8.4$ Hz, pyridine C_5-H, Ar), 8.09 (d, 2H, $J = 8.0$ Hz, Ar), 7.75 (d, 2H, $J = 7.6$ Hz, Ar), 7.47–7.49 (m, 4H, SO_2NH_2, Ar), 7.33 (d, 2H, $J = 7.2$ Hz, Ar), 2.41 (s, 3H, CH_3); ^{13}C NMR (100 MHz, DMSO-d_6): δ 155.8, 151.2, 145.4, 141.7, 140.6, 138.5, 135.8, 132.0, 129.7, 129.4, 128.5, 127.1, 124.6, 121.2, 112.7, 109.5, 20.9 (CH_3); ^{19}F NMR (376.4 MHz, DMSO-d_6): δ –58.69 (C_4-CF_3); DART-MS: *m/z* 587.12 $(M+H)^+$, $C_{26}H_{18}BrF_3N_4O_2SH^+$ calcd. 587.03.

(**8b**) Yield 11 %.

*4-[3-(4-Methylphenyl)-6-(2-naphthyl)-4-(trifluoromethyl)-1H-pyrazolo[3,4-b]pyridin-1-yl]benzenesulfonamide (**6i**)*

Yield 60 %; m.p. 298–300 °C; IR (KBr) cm^{-1}: 3379 & 3286 (m, N–H stretch), 1597 (s, C=N stretch), 1504 (m, N–H bend), 1342 and 1157 (s, SO_2 stretch); ^1H NMR (300 MHz, DMSO-d_6): δ 8.99 (s, 1H, pyridine C_5-H), 8.61 (d, 2H, $J = 8.7$ Hz, Ar), 8.50-8.53 (m, 2H, Ar), 8.11–8.18 (m, 4H, Ar), 8.00-8.03 (m, 1H, Ar), 7.61-7.64 (m, 2H, Ar), 7.52 (d, 2H, $J = 8.1$ Hz, Ar), 7.49 (s, ex, 2H, SO_2NH_2), 7.36 (d, 2H, $J = 8.1$ Hz, Ar), 2.44 (s, 3H, CH_3); ^{13}C NMR (75.5 MHz, DMSO-d_6): δ 157.4, 151.9, 145.9, 142.1, 141.2, 139.0, 134.4, 134.3, 133.3, 129.9, 129.5, 129.2, 129.0, 128.5, 128.0, 127.6, 127.2, 124.9, 121.7, 113.5, 109.7, 21.4 (CH_3); ^{19}F NMR (376.4 MHz, DMSO-d_6): δ –58.81 (C_4-CF_3); DART-MS: *m/z* 559.22 $(M+H)^+$, $C_{30}H_{21}F_3N_4O_2SH^+$ calcd. 559.13.

(**8b**) Yield: 12 %.

*4-[3-(4-Methylphenyl)-6-(2-thienyl)-4-(trifluoromethyl)-1H-pyrazolo[3,4-b]pyridin-1-yl]benzenesulfonamide (**6j**)*

Yield 60 %; m.p. 276–278 °C; IR (KBr) cm^{-1}: 3371 and 3271 (m, N–H stretch), 1597 (s, C=N stretch), 1504 (m, N–H bend), 1319 and 1134 (s, SO_2 stretch); ^1H NMR (400 MHz, DMSO-d_6): δ 8.51 (d, 2H, $J = 9.2$ Hz, Ar), 8.25-8.26 (m, 2H, pyridine C_5-H, thienyl), 8.07 (d, 2H, $J = 9.2$ Hz, Ar), 7.86 (d, 1H, $J = 4.8$ Hz, thienyl), 7.47 (d, 4H, $J = 9.2$ Hz, SO_2NH_2, Ar), 7.33 (d, 2H, $J = 8.0$ Hz, Ar), 7.26 (t, 1H, $J = 4.4$ Hz, thienyl), 2.41 (s, 3H, CH_3); ^{13}C NMR (100 MHz, DMSO-d_6): δ 152.5, 150.9, 145.6, 142.5, 141.6, 140.6, 138.5, 131.4, 129.5, 129.4, 129.1, 128.5, 126.9, 120.9, 111.7, 109.0, 20.9 (CH_3); ^{19}F NMR (376.4 MHz, DMSO-d_6): δ –58.82 (C_4-CF_3); DART-MS: *m/z* 515.15 $(M+H)^+$, $C_{24}H_{17}F_3N_4O_2S_2H^+$ calcd. 515.07.

(**8b**) Yield 12 %.

*4-[3-(4-Chlorophenyl)-6-methyl-4-(trifluoromethyl)-1H-pyrazolo[3,4-b]pyridin-1-yl]benzenesulfonamide (**7a**)*

Yield 60 %; m.p. 252–253 °C; IR (KBr) cm^{-1}: 3364 and 3271 (m, N–H stretch), 1597 (s, C=N stretch), 1504 (m, N–H bend), 1319 & 1126 (s, SO_2 stretch); ^1H NMR (300 MHz, DMSO-d_6): δ 8.48 (d, 2H, $J = 8.7$ Hz, Ar), 8.04 (d, 2H, $J = 8.7$ Hz, Ar), 7.79 (s, 1H, pyridine C_5-H), 7.60 (d, 4H, $J = 8.4$ Hz, Ar), 7.47 (s, ex, 2H, SO_2NH_2), 2.81 (CH_3); ^{13}C NMR (75.5 MHz, DMSO-d_6): δ 161.4, 151.6, 144.4, 142.3, 141.1, 134.5, 131.9, 128.5, 127.4, 121.9, 116.9, 108.9, 25.1 (CH_3); ^{19}F NMR (376.4 MHz,

DMSO-d_6): δ –58.91 (C_4-CF_3); DART-MS: *m/z* 467.11 $(M+H)^+$, $C_{20}H_{14}ClF_3N_4O_2SH^+$ calcd. 467.04.

*N-[1-[4-(Aminosulfonyl)phenyl]-3-(4-chlorophenyl)-1H-pyrazol-5-yl]acetamide (**8c**)*

Yield 17 %; m.p. 270–271 °C; IR (KBr) cm^{-1}: 3271 (m, N–H stretch), 1666 (s, C=O stretch), 1597 (s, C=N stretch), 1327 and 1157 (s, SO_2 stretch); ^{1}H NMR (300 MHz, DMSO-d_6): δ 10.20 (s, ex, 1H, NHCO), 7.96 (d, 2H, $J = 8.4$ Hz, Ar), 7.90 (d, 2H, $J = 8.4$ Hz, Ar), 7.80 (d, 2H, $J = 8.4$ Hz, Ar), 7.48–7.50 (m, 4H, SO_2NH_2, Ar), 6.96 (s, 1H, pyrazole C_4-H), 2.03 (s, 3H, NHCO*CH*$_3$); ^{13}C NMR (75.5 MHz, DMSO-d_6): δ 169.5 (NHCO), 150.2, 143.1, 141.4, 138.4, 133.2, 131.8, 129.2, 127.4, 127.3, 123.9, 100.9, 23.3 (NHCO*CH*$_3$).

*4-[3-(4-Chlorophenyl-4,6-bis(trifluoromethyl)-1H-pyrazolo[3,4-b]pyridin-1-yl]benzenesulfonamide (**7b**)*

Yield 70 %; m.p. 230–231 °C; IR (KBr) cm^{-1}: 3387 and 3279 (m, N–H stretch), 1597 (s, C=N stretch), 1504 (m, N–H bend), 1335 and 1149 (s, SO_2 stretch); ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.41 (d, 2H, $J = 8.4$ Hz, Ar), 8.28 (s, 1H, pyridine C_5-H), 8.09 (d, 2H, $J = 8.4$ Hz, Ar), 7.65 (s, 4H, Ar), 7.50 (s, ex, 2H, SO_2NH_2); ^{13}C NMR (75.5 MHz, DMSO-d_6): δ 150.0, 146.2, 145.8, 144.3, 142.6, 139.8, 134.4, 133.0, 132.8, 131.5, 130.5, 128.2, 127.1, 123.4, 122.2, 121.8, 113.0, 112.2; ^{19}F NMR (376.4 MHz, DMSO-d_6): δ –58.59 (C_4-CF_3), –65.45 (C_6-CF_3); DART-MS: *m/z* 521.10 $(M+H)^+$, $C_{20}H_{11}ClF_6N_4O_2SH^+$ calcd. 521.01.

(**8c**) Yield 12 %.

*4-[3-(4-Chlorophenyl)-6-phenyl-4-(trifluoromethyl)-1H-pyrazolo[3,4-b]pyridin-1-yl]benzenesulfonamide (**7c**)*

Yield 58 %; m.p. 238–240 °C; IR (KBr) cm^{-1}: 3333 and 3194 (m, N–H stretch), 1597 (s, C=N stretch), 1504 (m, N–H bend), 1335 and 1165 (s, SO_2 stretch); ^{1}H NMR (300 MHz, DMSO-d_6): δ 8.56 (d, 2H, $J = 8.7$ Hz, Ar), 8.33–8.36 (m, 3H, pyridine C_5-H, Ar), 8.10 (d, 2H, $J = 8.7$ Hz, Ar), 7.80 (d, 2H, $J = 8.4$ Hz, Ar), 7.62–7.65 (m, 3H, Ar), 7.48–7.50 (m, 4H, SO_2NH_2, Ar); ^{13}C NMR (100 MHz, $CDCl_3$/DMSO-d_6): δ 157.3, 151.8, 144.0, 141.6, 140.7, 136.7, 134.3, 131.0, 130.5, 128.9, 128.4, 127.9, 127.4, 126.9, 126.7, 126.6, 123.2, 120.8, 113.2, 109.1; ^{19}F NMR (376.4 MHz, DMSO-d_6): δ –58.76 (C_4-CF_3); DART-MS: *m/z* 529.16 $(M+H)^+$, $C_{25}H_{16}ClF_3N_4O_2SH^+$ calcd. 529.06.

(**8c**) Yield 21 %.

*4-[3-(4-Chlorophenyl)-6-(4-methylphenyl)-4-(trifluoromethyl)-1H-pyrazolo[3,4-b]pyridin-1-yl]benzenesulfonamide (**7d**)*

Yield 58 %; m.p. 258–260 °C; IR (KBr) cm^{-1}: 3350 and 3271 (m, N–H stretch), 1597 (s, C=N stretch), 1497 (m, N–H bend), 1327 and 1157 (s, SO_2 stretch); ^{1}H NMR (300 MHz, DMSO-d_6): δ 8.54 (d, 2H, $J = 8.7$ Hz, Ar), 8.32-8.36 (m, 3H, pyridine C_5-H, Ar), 8.09 (d, 2H, $J = 8.7$ Hz, Ar), 7.80 (d, 2H, $J = 8.7$ Hz, Ar), 7.64 (s, 4H, Ar), 7.51 (s, ex, 2H, SO_2NH_2), 2.50 (s, 3H, CH_3); ^{13}C NMR (75.5 MHz, DMSO-d_6): δ 157.8, 156.6. 151.8, 144.6, 142.3, 142.2, 141.4, 141.0, 140.9, 134.5, 134.3, 132.5, 131.9, 131.7, 130.2, 128.6, 128.1, 127.5, 125.2, 121.9, 121.8, 113.4, 109.4, 21.4 (CH_3); ^{19}F NMR (376.4 MHz, DMSO-d_6): δ −58.80 (C_4-CF_3); DART-MS: *m/z* 543.16 $(M+H)^+$, $C_{26}H_{18}ClF_3N_4O_2SH^+$ calcd. 543.07.

(**8c**) Yield 20 %.

*4-[3-(4-Chlorophenyl)-6-(4-methoxyphenyl)-4-(trifluoromethyl)-1H-pyrazolo[3,4-b]pyridin-1-yl]benzenesulfonamide (**7e**)*

Yield 53 %; m.p. 262–264 °C; IR (KBr) cm^{-1}: 3340 and 3271 (m, N–H stretch), 1597 (s, C=N stretch), 1504 (m, N–H bend), 1358 and 1134 (s, SO_2 stretch); ^{1}H NMR (300 MHz, DMSO-d_6): δ 8.55 (d, 2H, $J = 8.7$ Hz, Ar), 8.35 (d, 2H, $J = 8.4$ Hz, Ar), 8.26 (s, 1H, pyridine C_5-H), 8.09 (d, 2H, $J = 8.7$ Hz, Ar), 7.62–7.64 (m, 4H, Ar), 7.50 (s, ex, 2H, SO_2NH_2), 7.14 (d, 2H, $J = 8.7$ Hz, Ar), 3.86 (OCH_3); ^{13}C NMR (100 MHz, $CDCl_3$/DMSO-d_6): δ 162.0, 156.9, 149.8, 144.0, 142.4, 140.9, 137.6, 133.0, 131.1, 128.3, 126.7, 126.5, 123.2, 114.8, 112.2, 108.6, 104.2, 55.2 (OCH_3); ^{19}F NMR (376.4 MHz, DMSO-d_6): δ −58.77 (C_4-CF_3); DART-MS: *m/z* 559.12 $(M+H)^+$, $C_{26}H_{18}ClF_3N_4O_3SH^+$ calcd. 559.07.

(**8c**) Yield 22 %.

*4-[3-(4-Chlorophenyl)-6-(4-fluorophenyl)-4-(trifluoromethyl)-1H-pyrazolo[3,4-b]pyridin-1-yl]benzenesulfonamide (**7f**)*

Yield 50 %; m.p. 220–222 °C; IR (KBr) cm^{-1}: 3302 & 3240 (m, N–H stretch), 1597 (s, C=N stretch), 1504 (m, N–H bend), 1311 and 1165 (s, SO_2 stretch); ^{1}H NMR (300 MHz, DMSO-d_6): δ 8.55 (d, 2H, $J = 8.7$ Hz, Ar), 8.48 (dd, 2H, $^4J_{HF} = 5.4$ Hz, $^3J_{HH} = 8.7$ Hz, Ar), 8.37 (s, 1H, pyridine C_5-H), 8.10 (d, 2H, $J = 8.7$ Hz, Ar), 7.67 (d, 2H, $J = 8.7$ Hz, Ar), 7.63 (d, 2H, $J = 8.7$ Hz, Ar), 7.51 (s, ex, 2H, SO_2NH_2), 7.45 (t, 2H, $J = 8.7$ Hz, Ar); ^{13}C NMR (100 MHz, $CDCl_3$/DMSO-d_6): δ 156.2, 151.0, 145.2, 142.4, 137.7, 132.9, 131.1,

129.8, 128.3, 126.7, 126.6, 125.0, 123.2, 120.6, 116.2, 115.8; ^{19}F NMR (376.4 MHz, DMSO-d_6): δ −58.75 (C_4-CF_3); DART-MS: *m/z* 547.15 $(M + H)^+$, $C_{25}H_{15}ClF_4N_4O_2SH^+$ calcd. 547.05.

(**8c**) Yield 24 %.

*4-[3,6-bis(4-Chlorophenyl)-4-(trifluoromethyl)-1H-pyrazolo[3,4-b]pyridin-1-yl]benzenesulfonamide (**7g**)*

Yield 56 %; m.p. 230–232 °C; IR (KBr) cm^{-1}: 3340 & 3271 (m, N–H stretch), 1597 (s, C=N stretch), 1504 (m, N–H bend), 1327 and 1157 (s, SO_2 stretch); ^{1}H NMR (300 MHz, DMSO-d_6): δ 8.54 (d, 2H, $J = 8.7$ Hz, Ar), 8.42 (d, 2H, $J = 8.7$ Hz, Ar), 8.36 (s, 1H, pyridine C_5-H), 8.09 (d, 2H, $J = 8.7$ Hz, Ar), 7.67 (d, 2H, $J = 8.7$ Hz, Ar), 7.61–7.64 (m, 4H, Ar), 7.52 (s, ex, 2H, SO_2NH_2); ^{13}C NMR (75.5 MHz, DMSO-d_6): δ 156.5, 151.7, 144.6, 142.3, 140.9, 136.3, 135.8, 134.6, 131.9, 131.6, 130.0, 129.6, 128.6, 127.6, 121.9, 113.6, 109.8; ^{19}F NMR (376.4 MHz, DMSO-d_6): δ –58.73 (C_4-CF_3); DART-MS: *m/z* 563.12 $(M+H)^+$, $C_{25}H_{15}Cl_2F_3N_4O_2SH^+$ calcd. 563.02.

(**8c**) Yield 20 %.

*4-[6-(4-Bromophenyl)-3-(4-chlorophenyl)-4-(trifluoromethyl)-1H-pyrazolo[3,4-b]pyridin-1-yl]benzenesulfonamide (**7h**)*

Yield 53 %; m.p. 270–272 °C; IR (KBr) cm^{-1}: 3350 and 3271 (m, N–H stretch), 1597 (s, C=N stretch), 1504 (m, N–H bend), 1335 and 1134 (s, SO_2 stretch); ^{1}H NMR (300 MHz, DMSO-d_6): δ 8.54 (d, 2H, $J = 8.7$ Hz, Ar), 8.37 (s, 1H, pyridine C_5-H), 8.35 (d, 2H, $J = 8.7$ Hz, Ar), 8.09 (d, 2H, $J = 8.7$ Hz, Ar), 7.81 (d, 2H, $J = 8.7$ Hz, Ar), 7.63-7.66 (m, 4H, Ar), 7.51 (s, ex, 2H, SO_2NH_2); ^{13}C NMR (75.5 MHz, DMSO-d_6): δ 156.6, 151.7, 144.6, 142.3, 140.9, 136.3, 134.6, 132.6, 131.9, 131.6, 130.3, 128.6, 127.6, 125.2, 121.9, 113.7, 109.9; ^{19}F NMR (376.4 MHz, DMSO-d_6): δ –58.73 (C_4-CF_3); DART-MS: *m/z* 607.05 $(M+H)^+$, $C_{25}H_{15}BrClF_3N_4O_2SH^+$ calcd. 606.97.

(**8c**) Yield 24 %.

*4-[3-(4-Chlorophenyl)-6-(2-naphthyl)-4-(trifluoromethyl)-1H-pyrazolo[3,4-b]pyridin-1-yl]benzenesulfonamide (**7i**)*

Yield 48 %; m.p. 262–265 °C; IR (KBr) cm^{-1}: 3333 and 3186 (m, N–H stretch), 1597 (s, C=N stretch), 1504 (m, N–H bend), 1335 and 1165 (s, SO_2 stretch); ^{1}H NMR (300 MHz, DMSO-d_6): δ 9.00 (s, 1H, pyridine C_5-H), 8.61 (d, 2H, $J = 8.7$ Hz, Ar), 8.51 (d, 2H, $J = 8.7$ Hz, Ar), 8.11–8.16 (m, 4H, Ar), 7.98–8.02 (m, 1H, Ar), 7.59–7.69 (m, 6H, Ar), 7.51 (s, ex, 2H, SO_2NH_2); ^{13}C NMR (100 MHz, $CDCl_3$/DMSO-d_6): δ 157.1, 151.4, 144.1, 142.4, 141.5, 137.7, 134.3, 134.0, 133.8, 132.9, 130.9, 128.6, 128.3, 126.9, 126.7, 126.57, 126.51, 123.2, 120.7, 114.5, 109.9; ^{19}F NMR (376.4 MHz, DMSO-d_6): δ −58.77 (C_4-CF_3); DART-MS: *m/z* 579.15 $(M+H)^+$, $C_{29}H_{18}ClF_3N_4O_2SH^+$ calcd. 579.07.

(**8c**) Yield 25 %.

*4-[3-(4-Chlorophenyl)-6-(2-thienyl)-4-(trifluoromethyl)-1H-pyrazolo[3,4-b]pyridin-1-yl]benzenesulfonamide (**7j**)*

Yield 54 %; m.p. 268–270 °C; IR (KBr) cm^{-1}: 3340 and 3217 (m, N–H stretch), 1597 (s, C=N stretch), 1504 (m, N–H bend), 1335 and 1157 (s, SO_2 stretch); ^{1}H NMR (300 MHz, DMSO-d_6): δ 8.51 (d, 2H, $J = 8.7$ Hz, Ar), 8.32 (s, 1H, pyridine C_5-H), 8.30 (d, 1H, $J = 3.9$ Hz, thienyl), 8.07 (d, 2H, $J = 8.7$ Hz, Ar), 7.88 (d, 1H, $J = 5.1$ Hz, thienyl), 7.62-7.64 (m, 4H, Ar), 7.50 (s, ex, 2H, SO_2NH_2), 7.27-7.30 (m, 1H, thienyl); ^{13}C NMR (75.5 MHz, DMSO-d_6): δ 153.1, 151.3, 144.8, 142.8, 142.0, 141.0, 134.5, 131.9, 131.8, 131.5, 130.0, 129.6, 128.5, 127.4, 121.4, 113.0, 109.3; ^{19}F NMR (376.4 MHz, DMSO-d_6): δ –58.86 (C_4-CF_3); DART-MS: *m/z* 535.15 $(M+H)^+$, $C_{23}H_{14}ClF_3N_4O_2S_2H^+$ calcd. 535.01.

(**8c**) Yield 22 %.

Antimicrobial assays

Determination of antimicrobial activity (bacteria and yeasts)

The antimicrobial activity of thirty synthesized pyrazolo[3,4-*b*]pyridines was evaluated in vitro by agar well diffusion method (Ahmad and Beg, 2001; Andrews, 2001). All the microbial cultures were adjusted to 0.5 McFarland standard, which is visually comparable to a microbial suspension of approximately 1.5×10^8 cfu/mL. Twenty milliliter of Mueller–Hinton agar medium was poured into each petri plate and the agar plates were swabbed with 100 µL inocula of each test bacterium and kept for 15 min for adsorption. Using sterile cork borer of 8 mm diameter, wells were bored into seeded agar plates and these were loaded with a 100 µL volume with concentration of 4.0 mg/mL of each compound reconstituted in dimethylsulphoxide (DMSO). All the plates were incubated at 37 °C for 24 h. Antimicrobial activity of each compound was evaluated by measuring the zone of growth inhibition against the test microorganisms with zone reader (HiAntibiotic zone scale). DMSO was used as a negative control whereas ciprofloxacin was used as positive control for bacteria and amphotericin-B for fungal yeasts. This procedure was performed in three replicate plates for each organism.

Determination of minimum inhibitory concentration (MIC)

MIC is the lowest concentration of an antimicrobial compound that will inhibit the visible growth of a microorganism after overnight incubation. MIC of newly synthesized pyrazolopyridines against bacterial and yeast strains was tested through a modified agar well-diffusion method (Okeke *et al.*, 2001). In this method, a twofold serial dilution of each tested compound was prepared by first reconstituting the compound in DMSO followed by dilution in sterile distilled water to achieve a decreasing concentration range of 256–0.5 μg/mL. A 100 μL volume of each dilution was introduced into wells (in triplicate) in the agar plates already seeded with 100 μL of standardized inoculum (10^6 cfu/mL) of the test microbial strain. All test plates were incubated aerobically at 37 °C for 24 h and observed for the inhibition zones. MIC, shown by a clear zone of inhibition, was recorded for each test organism. Ciprofloxacin (bacteria) and amphotericin-B (yeasts) were used as positive control while DMSO as negative control.

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Conflict of interest The authors declare that they have no conflict of interest.

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