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Facile synthesis, ex-vivo and in vitro screening of 3-sulfonamide derivative of 5-(4-chlorophenyl)-1-(2,4-dichlorophenyl)-4-methyl-1*H*-pyrazole-3-carboxylic acid piperidin-1-ylamide (SR141716) a potent CB1 receptor antagonist

Brijesh Kumar Srivastava [a,*,†], Rina Soni [a], Jayendra Z. Patel [a], Satadru Jha [a,‡], Sandeep A. Shedage [a], Neha Gandhi [b,§], Kalapatapu V. V. M. Sairam [b], Vishwanath Pawar [c], Nisha Sadhwani [d], Prasenjit Mitra [d], Mukul R. Jain [c], Pankaj R. Patel [a]

[a] Department of Medicinal Chemistry, Zydus Research Centre, Cadila Healthcare Ltd., Sarkhej-Bavla N. H.8A, Moraiya, Ahmedabad 382210, India
[b] Department of Bio-informatics, Zydus Research Centre, Cadila Healthcare Ltd., Sarkhej-Bavla N. H.8A, Moraiya, Ahmedabad 382210, India
[c] Department of Pharmacology, Zydus Research Centre, Cadila Healthcare Ltd., Sarkhej-Bavla N. H.8A, Moraiya, Ahmedabad 382210, India
[d] Department of Cell-Biology, Zydus Research Centre, Cadila Healthcare Ltd., Sarkhej-Bavla N. H.8A, Moraiya, Ahmedabad 382210, India

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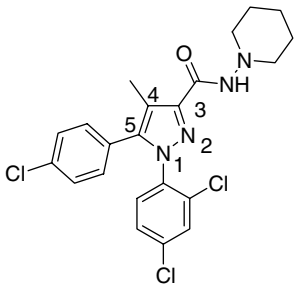
ABSTRACT

Facile synthesis of biaryl pyrazole sulfonamide derivative of 5-(4-chlorophenyl)-1-(2,4-dichlorophenyl)-4-methyl-1*H*-pyrazole-3-carboxylic acid piperidin-1-ylamide (SR141716, **1**) and an investigation of the effect of replacement of the –CO group in the compound **1** by the $-SO_2$ group in the aminopiperidine region is reported. Primary ex-vivo pharmacological testing and in vitro screening of sulfonamide derivative **2** showed the loss of CB1 receptor antagonism.

Pyrazole class of compounds are of great significance and have been extensively used for different therapeutics.[1] The biaryl pyrazole 5-(4-chlorophenyl)-1-(2,4-dichlorophenyl)-4-methyl-1*H*-pyrazole-3-carboxylic acid piperidin-1-ylamide **1** (SR141716, Fig. 1) is an interesting ligand in the drug development program to treat obesity and associated metabolic disorders.[2]

The compound **1** acts as CB1 receptor antagonist and was recently approved in Europe as Accomplia®.[3] A number of reports have been published with a pace to establish the structure–activity relationship (SAR) for every position of pyrazole ring of rimonabant.[1b,4–11] In compound **1** the carboxamide functionality on the 3rd position of the pyrazole is crucial for its therapeutic role as well as for its interactions with key amino acid residue K3.28 (192), as shown in the molecular modeling studies using the homology model.[5]

However, no work has been published for the replacement of the –CO group of the pyrazole ring of the compound **1** by the $-SO_2$ group. Most of the literature cites the sulfonation on the 5th position of the pyrazole nucleus,[12] however, there is scarcity



1
Rimonabant (SR141716)

Figure 1. Potent CB1 receptor antagonist.

* Corresponding author. Tel.: +91 2717 250801; fax: +91 2717 250606.
E-mail addresses: brijeshsrivastava@zyduscadila.com, bksri2000@yahoo.com (B. Kumar Srivastava).
† ZRC communication # 245.
‡ Present address: Department of Organic Chemistry, Indian Institute of Science, Bangalore, India.
§ Present address: Western Australian Biomedical Research Institute, Curtin University of Technology, Perth, Australia.

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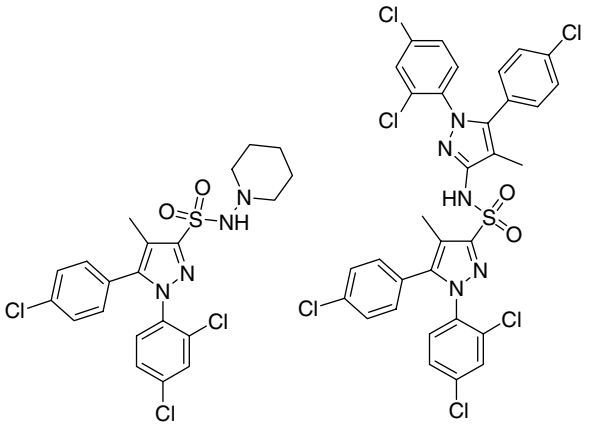


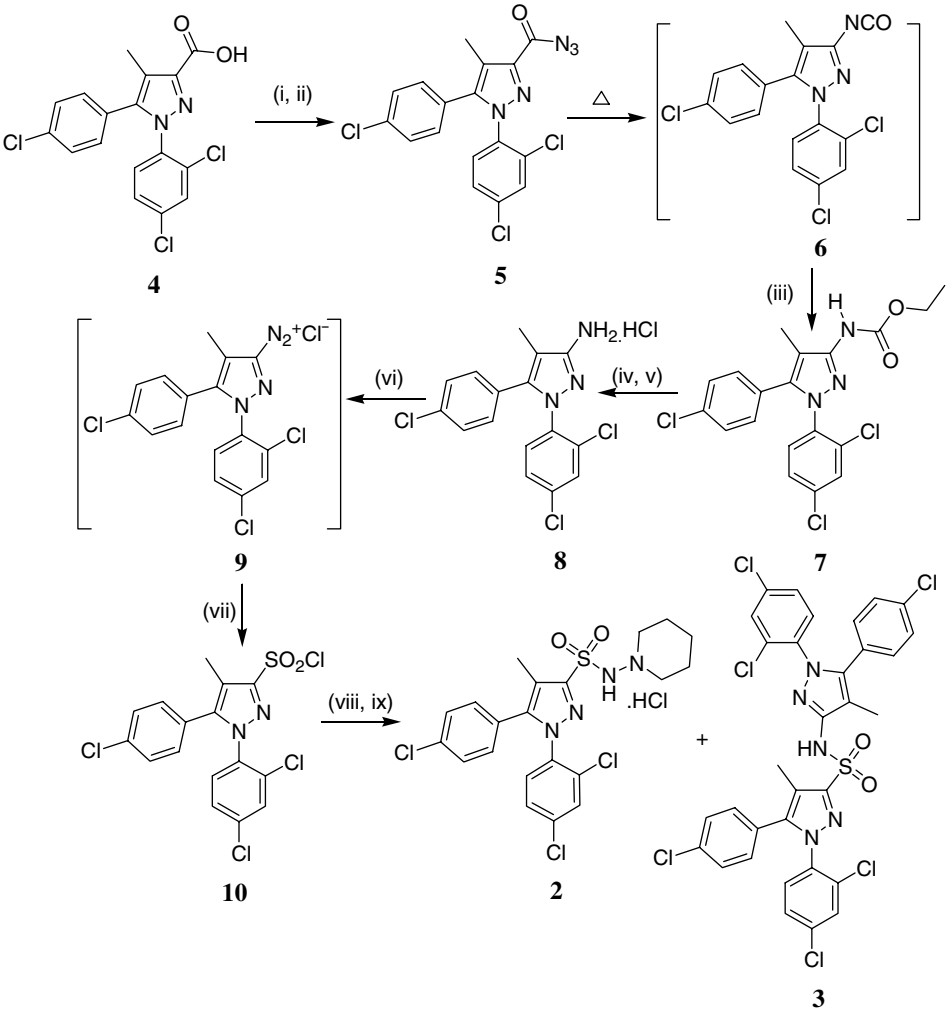
Figure 2. Novel Sulfonamide derivatives of rimonabant.

in the data for the sulfonation on the 3rd position of the pyrazole nucleus.

In the continuation of our cannabinoid research[13–21] herein, we explored the 3rd position of 1,5-diaryl pyrazole system of the compound **1** and opted to replace the –CO group of the carboxamide by the $-SO_2$ group. In this letter, we describe the synthesis, molecular modeling, and ex-vivo screening of the sulfonamide derivatives **2** and **3** (Fig. 2) in a mouse vas deferens assay, and in vitro cAMP hCB1 functional assay for assessing cAMP activity (Table 3).[22,23] The synthesis of sulfonamide derivative **2**, isolation and identification of bipyrazole sulfonamide derivative **3** have been depicted in the Scheme 1.[24]

In order to validate the rationale for the modification on the 3rd position of pyrazole nucleus in compound **1**, the structures **1** and **2** were docked using CFF and random Monte-Carlo simulations in the binding site as reported in our previous communication.[16] Docking analysis was observed on the basis of PLP (piece-wise linear potential) scores and hydrogen bonds of the ligands in the homology model of CB1 (Table 1). The poses were ranked with PLP-1, PLP-2, Dock score, and the conformations with the best scores were checked visually.

From modeling studies, energy-minimized structures and the PLP values (Table 1) of compound **1** and sulfonamide derivative **2**, it is clear that both orientate similarly (Fig. 3) and the oxygen of the carboxamide of **1** and sulfonamide of **2** form hydrogen bonds with the Lys192. At the same time the PLP scores suggest favorable binding of sulfonamide derivative **2** (PLP scores are in the arbitrary units of energy and lower PLP scores indicate better ligand binding, thus higher pK_i values).



Scheme 1. Reagents and conditions : (i) $(COCl)_2$, CH_2Cl_2, −20 to 25 °C, 2 h; (ii) TBAB, CH_2Cl_2, aq NaN_3, 0–5 °C, 2–3 h; (iii) EtOH, 78–80 °C, 5 h; (iv) 10% aq NaOH, EtOH, 80–82 °C, 5 h; (v) MeOH, ethereal·HCl, 0–5 °C, 1 h; (vi) aq $NaNO_2$, concd HCl, AcOH, HCOOH, −8 to −6 °C, 20 min; (vii) AcOH, concd HCl, $CuCl_2{\cdot}2H_2O$, SO_2, 25–27 °C, 30 min; (viii) *N*-aminopiperidine, CH_2Cl_2, NEt_3, 0–25 °C, 30 min; (ix) MeOH, ethereal·HCl, 0–5 °C, 1 h.

Table 1
Results of modeling of the homology model of CB1 with compound **1** and sulfonamide derivative **2**

Compound	PLP-1	PLP-2
2	−71.62	−67.84
1	−70.58	−65.75

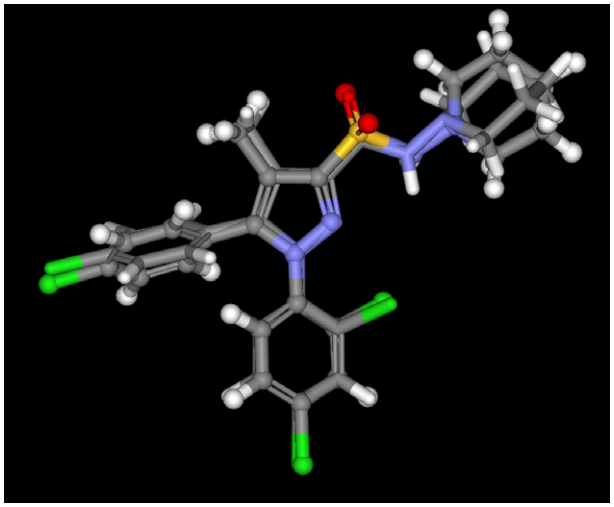


Figure 3. Superimposition of energy-minimized structure of molecule **2** (Ball and stick model) with **1** (Stick model).

The 1,5-diarylpyrazole-3-carboxylic acid **4** was synthesized as per literature procedure.[5] The sulfonamide derivative **2** was synthesized as depicted in Scheme 1. The method comprised the reaction of 1,5-diarylpyrazole-3-carboxylic acid **4** with oxalyl chloride to afford acid chloride derivative which was taken in dichloromethane with sodium azide under phase transfer conditions using tetrabutyl ammonium bromide to furnish the 1,5-diarylpyrazole-3-carboxazide derivative **5**.[25] The 1,5-diarylpyrazole-3-carboxazide derivative **5** thus obtained was converted to 1,5-diarylpyrazole-3-carbamate derivative **7** *via* formation of isocyanate **6**. The carbamate derivative **7** rearranged to 3-amino-1,5-diarylpyrazole derivative **8** under basic condition.[26] Finally, the 3-amino-1,5-diarylpyrazole derivative **8** was diazotized to afford diazonium salt **9**, which was subsequently reacted with gaseous sulfur dioxide to afford sulfonyl chloride derivative **10**.[27] The sulfonyl chloride derivative **10** was coupled with *N*-aminopiperidine to afford 1,5-diaryl-3-sulfonamide derivative **2**. The column-chromatography of the final reaction mixture afforded an impurity **3**, which was also subjected to ex-vivo and in vitro screening (Tables 2, 3 and Fig. 4).

Table 2
Ex-vivo screening of compounds **2**, **3**, and **1** against mouse vas deferens assay

Compound	Concentration (μM)	IC_{50} value of WIN-55212-2[a] (μM)
Control[b]	—	0.02 ± 0.01
2	10	0.12 ± 0.04
3	10	0. 32 ± 0.11
1	1	3.27 ± 0.87

[a] Values indicate the mean ± SEM obtained using three different tissue preparations of mouse vas deferens for the three tissues and IC_{50} (concentration of WIN-55212-2 required to produce 50% inhibition of contractile response) values were calculated from nonlinear regression (sigmoidal dose–response) curve fit analysis using Graph pad Prizm 4 software.

[b] 1% v/v DMSO and 5% v/v Tween 80 in water.

Table 3
In vitro hCB1 functional assay for assessing cAMP activity for compounds **2**, **3**, and **1**

Compound	Concentration (μM)	hCB1 (cAMP)[a] pmol/μg protein
DMSO		0.04 ± 0.00
Forskolin	10	10.01 ± 0.54
WIN-55212-2	100	3.10 ± 0.05
2	10	0.12 ± 0.04
3	10	0.09 ± 0.02
1	10	13.15 ± 0.42

[a] Values indicate mean ± SD performed in duplicate and the results being representative of at least three independent experiments.

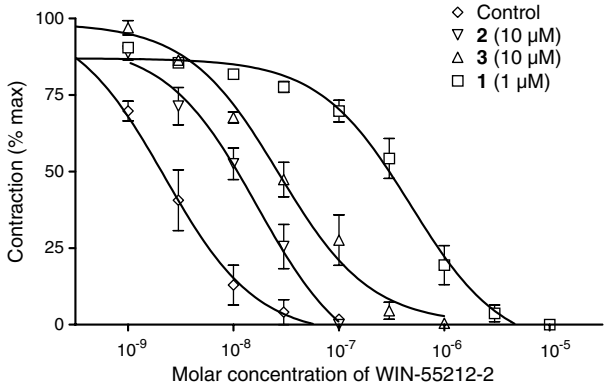


Figure 4. Effect of WIN-55212-2 on electrically evoked contractions of the mouse vas deferens in the presence of **1**, **2**, and **3**. Each point corresponds to the mean ± SEM obtained using three different tissue preparations of mouse vas deferens.

We also propose the condition under which bipyrazole sulfonamide derivative **3** might be formed. In fact, there is no quantification for the conversion of amino derivative **8** to its corresponding diazonium derivative **9**, since its unstable nature and at the same time the amino derivative **8** remaining as such in the reaction mixture competes with aminopiperidine and virtually attacks on the sulfonyl chloride derivative **10**, thereby forming the bipyrazole sulfonamide derivative **3**.

The CB1 receptor antagonists in the dose-dependent manner produce inhibition of electrically evoked contractions of the mouse vas deferens.[23] The WIN-55212-2 produced concentration-related inhibition of electrically evoked contractions of the mouse vas deferens in presence of vehicle (Fig. 4 and Table 2). The IC_{50} value of WIN-55212-2 in the presence of vehicle was 0.02 ± 0.01 μM. At a concentration of 1 μM, the compound **1** behaved as a competitive surmountable antagonist of WIN-55212-2 producing parallel rightward shift.

At a concentration of 10 μM the compounds **2** and **3** produced slight dextral shift of WIN-55212-2 indicative of weak antagonistic activity. The IC_{50} values of WIN-55212-2 in the presence of ligands **2** and **3** were 0.12 ± 0.04 and 0.32 ± 0.11 μM, respectively. We further tested the compounds **2** and **3** in hCB1 (cAMP)assay.[15] The compounds **2** and **3** did not respond significantly in the forskolin-stimulated cAMP assay as compared to positive control **1** (Table 3) and unlike **1** none of the compounds rescued 100 μM WIN-55212-2 mediated decrease of forskolin-induced cyclic AMP generation. Supporting the fact that replacement of the –CO group of the carboxamide region in the rimonabant by the $–SO_2$ group influences the antagonism activity and results in inferior antagonistic activity.

In summary, the introduction of $–SO_2$ group at 3rd position of 1,5-diarylpyrazole core structure of rimonabant was successfully obtained by employing the conventional Curtius reaction and is re-

ported for the first time. The isolation and characterization of the bipyrazole sulfonamide derivative **3** justified the loss in the yield of reaction during the formation of targeted sulfonamide derivative **2**.

Preliminary ex-vivo experiments and the results of in vitro cAMP hCB1 functional assay showed a loss of CB1 receptor antagonism for **2** compared to rimonabant, suggesting a misfitting of the bulky $-SO_2$ group in place of the –CO group and this in spite of the favorable PLP values and docking scores. However, at this stage the other factors contributing for the loss of CB1 receptor antagonism cannot be ruled out.

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22. *Ex-vivo mouse vas deferens assay:* Vas deferens of Swiss Albino Mice weighing 30–45 g was isolated. Tissues were mounted in bath containing Kreb's Hanseleit (Mg free) solution at 32 ± 1 °C and aerated with carbogen. The composition of the Krebs solution was (mM): NaCl 118.2, KCl 4.75, KH_2PO_4 1.19, $NaHCO_3$ 25.0, glucose 11.0, and $CaCl_2.6H_2O$ 2.54. Isometric contractions were evoked by stimulation with 0.9 s trains of three pulses of 110% maximal voltage (train frequency 0.1 Hz; pulse duration 0.9 ms) through a platinum electrode attached to the upper end and a stainless steel electrode attached to the lower end of each bath. Contractile response was recorded using Spel Isosys computer aided data acquisition system (Experimetria, Hungary). Concentration response curve of WIN-55212-2 was taken in presence of control, **1**, **2**, and **3** using three different tissue preparations of mouse vas deferens. WIN-55212-2 was dissolved in 5% v/v Tween 80 in water, and test compounds were dissolved in 1% v/v DMSO and 5% v/v Tween 80 in water. Further dilutions were achieved by adding water both to the stock solution of WIN-55212-2 and test compounds.
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24. Procedures for synthesis of compounds **5**, **7**, **8**, **2**, and **3**: Synthesis of 5-(4-chlorophenyl)-1-(2,4-dichlorophenyl)-4-methyl-1*H*-pyrazole-3-carbonyl azide **5**: The 5-(4-chlorophenyl)-1-(2,4-dichlorophenyl)-4-methyl-1*H*-pyrazole-3-carboxylic acid **4** (1.2 g, 3.14 mmol) was taken in dichloromethane (12 mL) to which oxalyl chloride (0.35 mL, 4.08 mmol) was added drop wise at −20 °C. The solution was stirred at 0–5 °C for 30 min and stirred at 25–27 °C for a period of 1 h. The progress of the reaction was monitored by TLC using 5% methanol in chloroform as a mobile phase. The solvents were evaporated on a rotatory evaporator under reduced pressure to afford an oil (1.25 g, 100%), which was dissolved in dichloromethane (14.5 mL) and to this tetrabutylammonium bromide (3.0 mg, 9.0 mmol) was added followed by addition of 35% aqueous sodium azide (1 mL) at 0 °C. The resulting mixture was stirred at 0–5 °C for 2 h. The progress of the reaction was monitored by TLC using 40% EtOAc in petroleum ether as a mobile phase. The organic layer was separated and washed with water (15 mL), and the dichloromethane layer was dried over anhydrous Na_2SO_4. The solvents were evaporated on a rotatory evaporator under reduced pressure and residue obtained was triturated in diisopropyl ether to get a solid. The solid was filtered on a Buchner funnel under suction and dried to afford the title compound **5** as brown solid (1.18 g, 92%); 99.01% purity by HPLC; mp 106–107 °C; ^{1}H NMR (300 MHz, DMSO-d_6): δ 7.80 (d, J = 1.89 Hz, 1 H), 7.73 (d, J = 8.52 Hz, 1H), 7.60–7.57 (dd, J = 8.43 and 1.98 Hz, 1H), 7.47 (d, J = 8.34 Hz, 2H), 7.24 (d, J = 8.34 Hz, 2H), 2.25 (s, 3H); IR (KBr) 3425, 2129, 1693, 1492 cm^{-1}; ESI-MS: 407 [M+H]$^+$; Anal. calcd for $C_{17}H_{10}Cl_3N_5O$: C 50.21%, H 2.48%, N 17.22%; found: C 50.07%, H 2.46%, N 17.04%.
Synthesis of [5-(4-chlorophenyl)-1-(2,4-dichlorophenyl)-4-methyl-1*H*-pyrazol-3-yl]-carbamic acid ethyl ester **7**: The 5-(4-chlorophenyl)-1-(2,4-dichlorophenyl)-4-methyl-1*H*-pyrazole-3-carbonyl azide **5** (3.39 g, 8.34 mmol) in ethanol (16.9 mL) was refluxed at 78–80 °C for a period of 5 h. The progress of the reaction mixture was monitored by TLC using 30% EtOAc in petroleum ether as a mobile phase. To the reaction mixture was added H_2O (17 mL) at 0–5 °C and stirred at 0–5 °C for over a period of 16–18 h. The solvents were evaporated on a rotatory evaporator under reduced pressure to afford an oily residue. The residue was dissolved in EtOAc (20 mL). The organic layer was washed with water (2 × 20 mL) followed by brine (20 mL), and the dichloromethane layer was dried over anhydrous Na_2SO_4. The solvents were evaporated on a rotatory evaporator under reduced pressure and the residue obtained was triturated in petroleum ether (10 mL) to afford solid. The solid was filtered on a Buchner funnel under suction and dried to afford the title compound **7** as yellow solid (3.1 g, 87%); 99.66% purity by HPLC; mp 150–152 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.39 (s, 1H), 7.30–7.24 (m, 5H), 7.07 (d, J = 8.46 Hz, 2H), 4.27–4.20 (q, 2H), 2.06 (s, 3H), 1.31 (t, 3H); IR (KBr) 3400, 3276, 1701, 1485 cm^{-1}; ESI-MS: 425 [M+H]$^+$; Anal. calcd for $C_{19}H_{16}Cl_3N_3O_2$: C 53.73%, H 3.80%, N 9.89%; found: C 53.19%, H 3.76%, N 9.79%.
Synthesis of 5-(4-chlorophenyl)-1-(2,4-dichlorophenyl)-4-methyl-1*H*-pyrazol-3-ylamine hydrochloride **8**: The [5-(4-chlorophenyl)-1-(2,4-dichlorophenyl)-4-methyl-1*H*-pyrazol-3-yl]-carbamic acid ethyl ester **7** (3.39 g, 7.99 mmol) was taken in ethanol (26 mL) to which 10% aqueous solution of NaOH (25.6 mL) was added and refluxed at 100 °C for a period of 5 h. The progress of the reaction was monitored by TLC using 5% methanol in chloroform as a mobile phase. The reaction mixture was neutralized by 10% dilute HCl at 0–5 °C. The solvents were removed on a rotatory evaporator under reduced pressure to afford oily residue. The residue was dissolved in EtOAc (25 mL) and organic layer was washed with water (2 × 25 mL) followed by brine (25 mL) and dried over anhydrous Na_2SO_4. The EtOAc layer was evaporated on a rotatory evaporator under reduced pressure to afford oil. The residue was taken in methanol (10 mL) to which ethereal HCl (2 mL) was added at 0–5 °C and stirred for 1 h. The solid precipitated was filtered on a Buchner funnel under suction and dried to afford the title compound **8** as off-white solid (2.2 g, 70%); 98.90% purity by HPLC; mp 234–236 °C; ^{1}H NMR (300 MHz, DMSO-d_6): δ 7.76 (s, 1H), 7.61–7.51 (m, 2H), 7.45 (d, J = 7.26 Hz, 2H), 7.20 (d, J = 7.20 Hz, 2H), 4.02–4.00 (br s, 2H), 2.03 (s, 3H); IR (KBr) 3423, 2894, 2563, 1492 cm^{-1}; ESI-MS: 352 [M+H−HCl]$^+$; Anal. calcd for $C_{16}H_{13}Cl_4N_3$: C 49.39%, H 3.37%, N 10.80%; found: C 48.84%, H 3.67%, N 10.65%.

Hydrochloride salt of 5-(4-chlorophenyl)-1-(2,4-dichlorophenyl)-4-methyl-1*H*-pyrazole-3-sulfonic acid piperidin-1-ylamide **2**: To a solution of 5-(4-chlorophenyl)-1-(2,4-dichlorophenyl)-4-methyl-1*H*-pyrazol-3-ylamine hydrochloride **8** (0.55 g, 1.41 mmol), acetic acid (2 mL), con. HCl (6.7 mL), and formic acid (6.7 mL) was added the 75% aqueous solution of sodium nitrite (0.3 mL) drop wise at −8 to −6 °C. The diazotized solution **9** was stirred for 10–15 min and then poured portion wise at 15 °C into a freshly prepared mixture of cupric chloride dihydrate (0.24 g, 1.41 mmol) and acetic acid (18.4 mL) saturated with sulfur dioxide. The mixture was stirred at 25–27 °C for 30–40 min. to afford sulfonyl chloride derivative **10**. The solvents were evaporated on a rotatory evaporator under reduced pressure to afford oily residue. The residue was dissolved in dichloromethane (10 mL). The organic layer was separated and washed with water (10 mL), and dried over anhydrous Na_2SO_4. The solvents were evaporated on a rotatory evaporator under reduced pressure to afford oily residue. The residue was dissolved in dichloromethane (10 mL) to which *N*-amino piperidine (0.26 mL, 1.89 mmol) was added followed by TEA (0.20 mL, 1.89 mmol) at 0–5 °C. The reaction mixture was stirred at 0–5 °C for over a period of 30 min. The progress of the reaction was monitored by TLC using 5% methanol in chloroform as a mobile phase. The organic layer was washed with water (10 mL) and dichloromethane layer was dried over anhydrous Na_2SO_4. The solvents were evaporated on a rotatory evaporator under reduced pressure to afford oily residue. The oily residue was purified through flash column-chromatography using petroleum ether: EtOAc (9:1) as an eluent. The fractions were pooled and solvents were evaporated on a rotatory evaporator under reduced pressure to afford oil. To a solution of oily residue in methanol (5 mL) was added ethereal HCl (1 mL) at 0–5 °C and stirred for 1 h. The solid precipitated was filtered on a Buchner funnel under suction and dried to afford the title compound **2** as off-white solid (0.15 g, 19%); 98.59% purity by HPLC; mp 146–147 °C; ^{1}H NMR (300 MHz, DMSO-d_6): δ 7.44 (d, J = 1.92 Hz, 1H), 7.31 (d, J = 8.48 Hz, 2H), 7.25 (d, J = 3.33 Hz, 2H), 7.07 (d, J = 8.45 Hz, 2H), 3.34–3.30 (br s, 4H), 2.28 (s, 3H), 1.68–1.65 (br s, 4H), 1.54–1.52 (br s, 2H); ^{13}CNMR (100 MHz, DMSO-d_6): δ 22.5, 23.2, 26.6, 56.26, 120.6, 128.3, 129.2, 130.2, 130.6, 131.4, 131.8, 133.7, 135.6, 136.7, 137.0, 138.6, 141.8; IR (KBr) 3440, 1496, 1338, 1163 cm^{-1}; ESI-MS: 538 [M]$^+$; Anal. calcd for $C_{21}H_{21}Cl_3N_4O_2S$: C 50.46%, H 4.23%, N 11.21%; found: C 49.75%, H 4.16%, N 11.06%.

Isolation and identification of 5-(4-chlorophenyl)-1-(2,4-dichlorophenyl)-4-methyl-1*H*-pyrazole-3-sulfonic acid [5-(4-chlorophenyl)-1-(2,4-dichlorophenyl)-4-methyl-1*H*-pyrazol-3-yl]-amide **3**: During the formation of 5-(4-chlorophenyl)-1-(2,4-dichlorophenyl)-4-methyl-1*H*-pyrazole-3-sulfonic acid piperidin-1-ylamide **2**, one of the major impurities formed was isolated through the column-chromatography using silica gel of 230-400 mesh and petroleum ether: EtOAc (9:1) as an eluent. The fractions were pooled and solvents were evaporated on a rotatory evaporator under reduced pressure to afford oil. The oil was triturated in petroleum ether (15 mL) to afford the brown solid (0.41 g, 37%); 96.12% purity by HPLC; mp 132–134 °C; ^{1}H NMR (300 MHz, DMSO-d_6):δ 10.44 (s, 1H), 7.77–7.73 (dd, J = 10.38 and 2.09 Hz, 2H), 7.64–7.57 (m, 2H), 7.55–7.50 (m, 2H), 7.46–7.41 (m, 4H), 7.16–7.12 (m, 4H), 2.05 (s, 3H), 1.93 (s, 3H); ^{13}CNMR (100 MHz, DMSO-d_6): δ 21.6, 22.8, 102.6, 118.6, 128.3, 129.6, 130.5, 130.8, 131.6, 132.1, 133.2, 135.6, 136.6, 136.8, 138.8, 139.6, 142.8, 158.6; IR (KBr) 3433, 1488, 1340, 1164 cm^{-1}; ESI-MS: 753 [M]$^+$; Anal. calcd for $C_{32}H_{21}Cl_6N_5O_2S$: C 51.09%, H 2.81%, N 9.31%; found: C 49.13%, H 2.71%, N 8.96%.

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