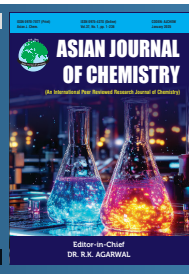
Asian Journal of Chemistry; Vol. 37, No. 6 (2025), 1315-1321

ASIAN JOURNAL OF CHEMISTRY

https://doi.org/10.14233/ajchem.2025.33717



Synthesis and Antimicrobial Activity of Novel Sulfonyl Piperidine Carboxamide Derivatives Prepared from *N*-Boc-Piperidine-3-carboxylic Acid *via* Amide Coupling

SHITAL JAGTAP[1] and POONAM KASWAN[2,*]

[1]Department of Chemistry, Annasaheb Magar College, Hadapsar, Pune-411028, India
[2]Department of Industrial Chemistry, AISSMS Institute of Information Technology, Pune-411001, India

*Corresponding author: E-mail: poonamcym@gmail.com

Received: 12 March 2025; *Accepted*: 21 April 2025; *Published online*: 27 May 2025; AJC-22003

Piperidines serve as pivotal synthetic building blocks in the realm of drug design, with their derivatives forming essential parts of a wide range of drugs and alkaloids. This study presents a novel approach involving sulfonyl derivatives of piperidine-3-carboxylic acid, achieved through amide coupling with substituted sulphonyl chlorides. The synthesized compounds underwent characterization *via* IR, ^{1}H NMR, ^{13}C NMR and MS analyses. Specifically, a series of novel sulphonamides derived from 1-(*tert*-butoxycarbonyl)piperidine-3-carboxylic acid was synthesized, given the significance of sulphonamides as a vital drug class. Antimicrobial activity screening against both Gram-positive and Gram-negative bacteria, as well as fungi, was evaluated. The MIC concentration results revealed moderate to good activity against Gram-positive and Gram-negative microorganisms and fungal organisms.

Keywords: Heterocycles, Piperidine, Amide, Sulphonyl chlorides.

INTRODUCTION

Amide coupling reactions stand as a cornerstone in organic synthesis, holding paramount importance as the most frequently employed reaction in the realm of pharmaceuticals [1-4]. The fundamental principle of amide coupling involves the reaction of an activated carboxylic acid with an amine [5-9]. The activated carboxylic acid acts as a reactive moiety, initiating the coupling process with the amine to generate the desired amide product [10-13]. Various coupling reagents are employed to facilitate and optimize the amide coupling reaction. Among these, HATU (1-[*bis*(dimethylamino)methylene]-1*H*-1,2,3-triazolo[4,5-*b*]-pyridinium3-oxidhexafluoro phosphate), DIPEA (*N*,*N*-diiso-propylethylamine) and DMF (dimethylformamide) constitute a well-known combination that enhances the efficiency and yield of the reaction [14,15]. These reagents collectively ensures the activation of carboxylic acid and facilitates the smooth coupling with amine, leading to the formation of the desired amide bond. Moreover, HBTA (N,N,N′,N′-tetramethyl-O-(1*H*-benzotriazol-1-yl)uranium hexafluorophosphate) is another coupling reagent commonly employed in amide coupling reactions [16-18]. In general, amide coupling reactions, facilitated by a variety of coupling reagents such as HATU, DIPEA, DMF and HBTA, serve as a linchpin in the synthesis of pharmaceutical compounds [19-21]. This synthetic strategy plays a pivotal role in the design and development of novel drugs, contributing to the advancement of medicinal chemistry and pharmaceutical research [22-25]. Several well-known drugs, including antifungal fenpropidin, anti-oomycete agent oxathiapiprolin, anti-Alzheimer drug donepezil and anticonvulsant agent ifenprodil, feature a piperidine link [26-29].

Some derivatives of piperidine containing a sulfonamide unit exhibit remarkable bioactivity. Because of their vast range of bioactivities, sulfonamide molecules have found extensive use in medicine [30-33]. Sulfonamide-based drugs have been developed to treat a wide range of bacterial illnesses. Sulfonamides can inhibit fungus, which makes them effective against fungal infections. The properties that have antiviral, anticancer, anti-inflammatory, antitumor and antimalarial activities [34-36]. Future research on the characteristics and mechanisms of sulfonamides may lead to advancements in medicine, particularly in drug development and therapeutic treatments [37-40]. Acknowledging the pivotal role played by the piperidine scaffold in the realm of medicinal chemistry, researchers have inve-

sted substantial efforts in formulating a multiple of synthetic protocols to generate diverse piperidine derivatives [41-45]. Among the noteworthy methods is the hydrogenation of pyridine, a process that enables the reduction of pyridine rings to yield piperidine structures. Another significant approach is the cyclocondensation of α-haloimines, facilitating the formation of piperidine rings through intramolecular cyclization. Moreover, a unique strategy involves the displacement reaction of pyran, resulting in the formation of a piperidine ring by displacing a pyran moiety. Widely adopted is the reduction of dihydropyridines, a method that finds broad application in synthesizing piperidine derivatives [46-50]. The aim is to synthesize compounds that not only excel in their primary function of combating microbial infections but also meet the rigorous standards of safety and tolerability required for successful clinical applications.

The present research aims to synthesize pharmacologically important compounds with potential efficacy against various Gram-negative and Gram-positive bacteria and fungi. The study considers the significance of amide coupling, incorporating the piperidine moiety with sulphonamide derivatives. The investigation evaluates the antimicrobial efficacy of a novel series of sulfanilamide derivatives containing piperidine fragments through amide coupling reactions against both Gram-positive and Gram-negative bacteria and fungi.

EXPERIMENTAL

For this work, Avra Laboratories and Sigma-Aldrich were the only commercial sources of the compounds and used without purification. Merck pre-coated silica gel 60 F_{254} aluminum sheets were used for TLC analysis, which was used to track the course of the reactions and the UV light was used to display the results. The melting points were measured using a Casia-Siamia (VMPAM) melting point apparatus and are uncorrected. Proton nuclear magnetic resonance (PMR), carbon-13 nuclear magnetic resonance (CMR), infrared (IR) and ESI-MS studies were used to characterize the final products. One Varian NMR spectrometer operating at 400 MHz was used to record ^{1}H NMR spectra, while another Varian NMR spectrometer operating at 100 MHz was used to record ^{13}C NMR spectra.

Procedure: Starting with *p*-chloroaniline, derivatives of 4-chlorophenyl)sulfonyl)piperidine-3-carboxamide (**9a-j**) were synthesized. A series of stages were involved in the synthetic process, such as amide coupling, deprotection and the formation of sulfonyl derivatives. The target compounds were synthesized using a variety of substituted sulfonyl chlorides.

Step-A: Synthesis of *tert*-butyl (2-((4-chlorophenyl)-amino)-2-oxoethyl)carbamate (3): 4-Chloroaniline (**1**, 5 g, 39.2 mmol) was dissolved in 25 mL of DMF in a reaction vessel with an inert atmosphere. HATU (22.4 g, 59.0 mmol) and DIPEA (20.6 mL, 118.1 mmol) were added to this solution followed by Boc-glycine (**2**, 8.27 g, 47.2 mmol) and then the reaction mixture was swirled at room temperature for 12 h. After that, the reaction mixture was poured over crushed ice with10 min stirring. Ethyl acetate (3.50 mL) was used to extract the crude product. Following the separation of organic layer, 50 mL of cold water and 50 mL of brine were used for washing. The crude product was obtained by drying the organic layer over anhydrous sodium sulfate and then concentrating it under low pressure. Using 70% ethyl acetate in hexane eluent, silica gel (100-200 mesh) column chromatography was used to purify the crude product. *tert*-Butyl(2-((4-chlorophenyl)amino)-2-oxo-ethyl)carbamate (**3**, 9.5 g, 85%) was obtained as pale yellow solid product.

Step-B: Synthesis of 2-amino-*N*-(4-chlorophenyl)acetamide (4): A solution of *tert*-butyl (2-((4-chlorophenyl)amino)-2-oxoethyl)carbamate (**3**, 9 g, 31.6 mmol) in dichloromethane (50 mL) was cooled to 0 ºC followed by the dropwise addition of 4 M HCl in dioxane (45 mL). The reaction mixture was stirred at room temperature for 4 h. The progress of the reaction was monitored by TLC. The reaction mixture was completely evaporated to dryness to afford crude product upon basification using aqueous Na_2CO_3 solution (50 mL). The crude product was extracted with DCM (2 × 50 mL). The organic layer was separated and washed with brine (50 mL) and the organic layer was evaporated under reduced pressure to afford 2-amino-N-(4-chlorophenyl)acetamide (**4**, 88% m.p.: 260 ºC) as brown solid.

Step-C: (4-Chlorophenyl)amino)-2-oxoethyl)carbamoyl)piperidine-1-carboxylate (6): To a solution of 2-amino-N-(4-chlorophenyl)acetamide (**4**, 5 g, 27.0 mmol) in DMF (25 mL), added HATU (15.4 g, 40.6 mmol), DIPEA (14.2 mL, 81.2 mmol) and piperidine-3-carboxylic acid (**5**, 7.44 g, 32.4 mmol). The reaction mixture was stirred at room temperature for 12 h. The progress of the reaction was monitored using TLC. The reaction mixture was poured into crushed ice and stirred for 10 min. The crude product was extracted with ethyl acetate (3.50 mL). The organic layer was collected and washed with 50 mL of cold water and 50 mL of brine. The separated organic layer was dried over anhydrous Na_2SO_4 and evaporated under reduced pressure to yield a crude product. The crude was purified by silica gel (100-200 mesh) column chromatography by using 70% ethyl acetate in hexane to afford (*tert*-butyl 3-((2-((4-chlorophenyl)amino)-2-oxoethyl)carbamoyl)piperidine-1-carboxylate (**6**, 8.5 g, 82%, m.p.: 168 ºC) as a yellow solid.

Step-D: Synthesis of (*N*-(2-((4-chlorophenyl)amino)-2-oxoethyl)piperidine-3-carboxamide (7): A solution of (*tert*-butyl 3-((2-((4-chlorophenyl)amino)-2-oxoethyl)carbamoyl) piperidine-1-carboxylate (**6**, 5 g, 12.6 mmol) in DCM (30 mL) was cooled to 0 ºC. Dropwise added 4 M HCl to dioxane (25 mL) under an inert atmosphere. The reaction mixture was stirred at room temperature for 4 h. After completing the starting material, completely dry the reaction mixture to obtain crude, which was basified with aqueous sodium carbonate solution (50 mL) and extracted with DCM (2 × 50 mL). The organic layer was separated and washed with brine (50 mL). The separated the organic layer and evaporated under reduced pressure, affording (*N*-(2-((4-chlorophenyl)amino)-2-oxoethyl)piperidine-3-carboxamide (**7**, 3.5 g, 94%, m.p.: 156 ºC) as brown solid.

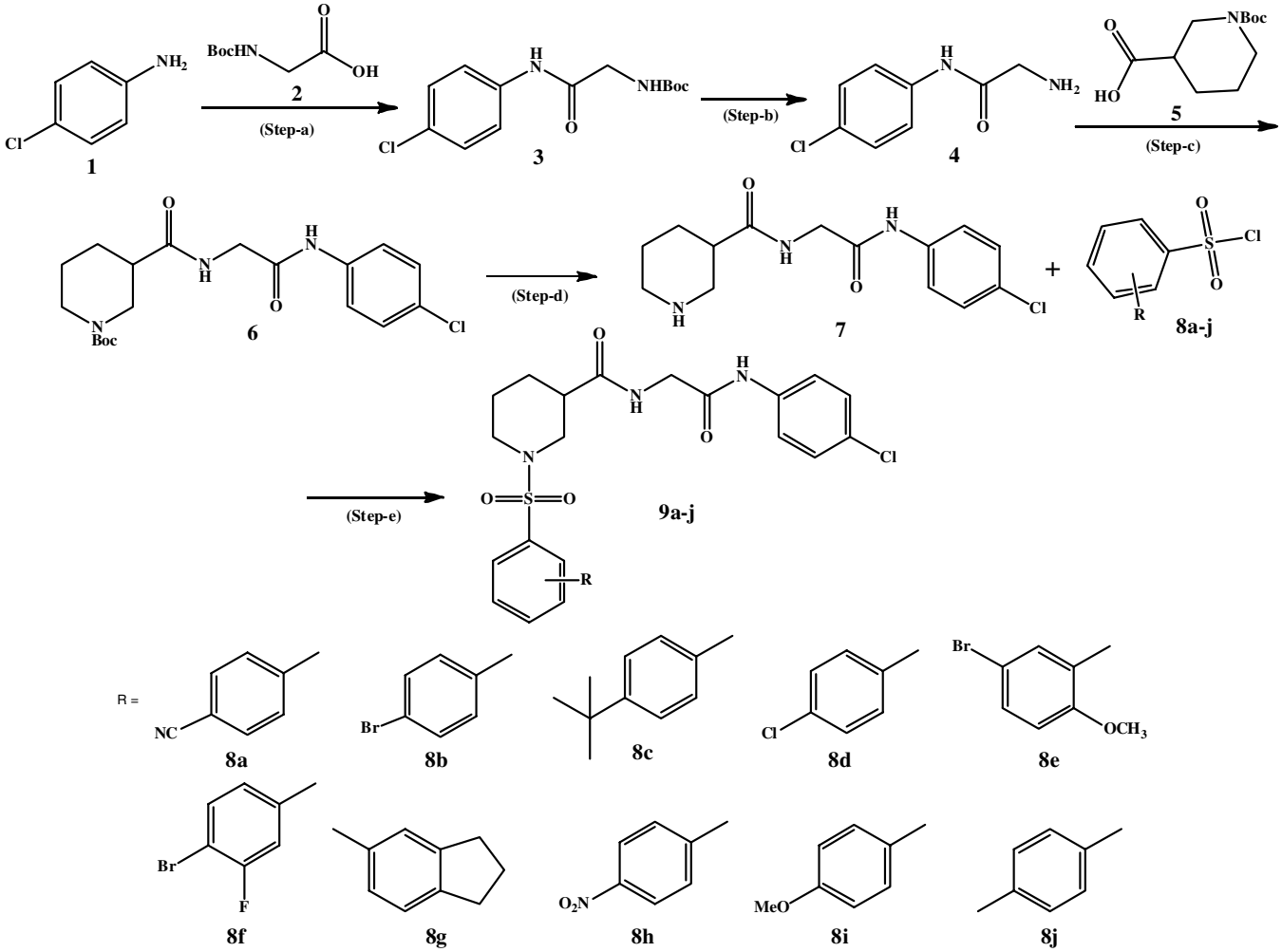
Step-E: General procedure for the synthesis of (*N*-(2-((4-chlorophenyl)amino)-2-oxoethyl)-1-((substituted phenyl)-sulfonyl)piperidine-3-carboxamide (9a-j): To a solution of (*N*-(2-((4-chlorophenyl)amino)-2-oxoethyl)piperidine-3-carboxamide (**7**, 1 equiv.) in DMF (5 vol.) was added DIPEA (3 vol.) at 0 ºC and stirred reaction mixture at the same temp-

erature for 15 min. Added substituted sulfonyl chlorides (**8a-j**) (1.2 equiv.) portionwise and stirred the reaction mixture at room temperature for 12 h. The progress of the reaction was monitored by TLC. The reaction mixture was poured on crushed ice to get precipitation and was filtered under reduced pressure. The solid product was washed with water (25 mL), cold diethyl ether (25 mL) and cold pentane (25 mL) to afford compounds (**9a-j**). The crude product was purified by column chromatography (silica, 100-200 mesh, 5-30% EtOAc in hexane) to afford *N*-(2-((4-chlorophenyl)amino)-2-oxoethyl)-1-((substituted-phenyl)sulfonyl)piperidine-3-carboxamide **(9a-j)** (**Scheme-I**).

***N*-(2-((4-Chlorophenyl)amino)-2-oxoethyl)-1-((4cyano-phenyl)sulfonyl)piperidine-3-carboxamide (9a):** Yellow solid; yield: 81%; m.p.: 134-135 ºC; IR (UATR, ν_{max}, cm^{-1}): 3313 (NH), 2957 (NH), 1491 (S=O), 2233 (C≡N), 1660 (C=O), 1537 (ArC=C), 829 (*p*-disubst.); ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 1.40-1.58 (m, 3H), 1.51-1.58 (m, 3H), 2.0 (d, 1H) 3.55 (t, 1H), 3.7 (d, 1H), 4.20 (m, 1H), 4.60 (d, 1H), 7.36 (d, *J* = 8.8 Hz, 2H), 7.60 (d, *J* = 8.8 Hz, 2H), 7.90 (d, *J* = 8.4 Hz, 2H), 8.06 (d, *J* = 8.4 Hz, 2H), 8.0 (d, *J* = 7.6 Hz, 1H), 10.14 (S, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ ppm: 27.32, 28.78, 29.58, 48.12, 56.90, 59.15, 120.13, 123.01, 125.99, 132.72, 132.10, 133.84, 138.39, 143.05, 148.85, 175.13, 176.28. MS *m/z* (%): 461.2 (M+H); HPLC: 96.4% RT: 6.39 min; Anal. calcd. (found) % for $C_{21}H_{21}ClN_4O_4S$; C, 54.72 (54.74); H, 4.59 (4.64); Cl, 7.69 (7.69); N, 12.16 (12.10); O, 13.88 (13.88); S, 6.96 (6.96).

1-((4-Bromophenyl)sulfonyl)-*N*-(2-((4-chlorophenyl)-amino)-2-oxoethyl)piperidine-3-carboxamide (9b): Yellow solid; yield: 70%; m.p.: 174-175 ºC; IR (UATR, ν_{max}, cm^{-1}): 3314 (NH), 2957 (NH), 1492 (S=O), 1658 (C=O), 1537 (ArC=C);^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 1.46-1.50 (m, 3H), 1.51-1.60 (m, 3H), 2.0 (d 1H), 3.55 (t, 1H), 3.7 (d, 1H), 4.25 (m, 1H), 4.58 (d, 1H), 7.78 (d, *J* = 8.8 Hz, 2H), 7.62 (d, *J* = 8.8 Hz, 2H), 7.67 (d, *J* = 8.4 Hz, 2H), 7.37 (d, *J* = 8.8 Hz, 2H), 8.16 (d, *J* = 7.6 Hz, 1H), 10.17 (S, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ ppm: 22.13, 23.47, 24.90, 43.13, 52.23, 54.38, 121.31, 126.87, 127.39, 129.10, 129.23, 132.58, 138.36, 139.54, 170.58, 171.57; MS *m/z* (%): 514.0 (M+H); HPLC: 97.1%, RT: 6.98 min; Anal. calcd. (found) % for $C_{20}H_{21}BrClN_3O_4S$; C, 46.66 (46.69); H, 4.11 (4.12); Br, 15.52 (15.52); Cl, 6.89 (6.89); N, 8.16 (8.21); O, 12.43 (12.43); S, 6.23 (6.23).

1-((4-(*tert*-Butyl)phenyl)sulfonyl)-*N*-(2-((4-chloro-phenyl)amino)-2-oxoethyl)piperidine-3-carboxamide (9c): Yellow solid; yield: 75%; m.p.: 141-142 ºC; IR (UATR, ν_{max},



Scheme-I: Synthesis of4-chlorophenyl)sulfonyl)piperidine-3-carboxamide (**9a-j**): Reagents and conditions: (a) HATU, DIPEA, DMF, 0 ºC-RT, 12 h; (b) 4 N HCl in dioxane, DCM, 0 ºC-RT, 4 h; (c) HATU, DIPEA, DMF, 0 ºC-RT, 12 h; (d) 4 N HCl in dioxane, 0 ºC-RT, 4 h; (e) substituted sulfonyl chloride (**8a-j**), DIPEA, DMF, 0 ºC-RT, 12 h

cm^{-1}): 3288 (NH), 2924 (NH), 1492 (S=O), 1156 (S=O), 1658 (C=O), 1536 (C=C); ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 1.32 (s, 9 H), 1.47-1.52 (m, 3H), 1.52-1.58 (m, 3H), 2.0 (d 1H), 3.65 (d, 2H), 4.35 (m, 1H), 4.58 (d, 1H), 7.78 (d, *J* = 8.8 Hz, 2H), 7.38 (d, *J* = 8.8 Hz, 2H), 7.68 (d, *J* = 8.8 Hz, 2H), 7.59 (d, *J* = 8.4 Hz, 2H), 7.71 (d, *J* = 8.4 Hz, 2H), 8.07 (d, *J* = 7.6 Hz, 1H), 10.15 (S, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ ppm: 22.13, 24.96, 23.47, 29.50, 43.03, 52.26, 54, 46, 126.35, 126.22, 128.96, 129.10, 132.72, 137.64, 138.31, 155.95, 170.80, 171.56. MS *m/z* (%): 492.5 (M+H); HPLC: 98.4%, RT: 6.21 min; Anal. calcd. (found) % for $C_{24}H_{30}ClN_3O_4S$; C, 58.59 (58.54); H, 6.15 (6.10); Cl, 7.21 (7.21); N, 8.54 (8.59); O, 13.01 (13.01); S, 6.52 (6.52).

***N*-(2-((4-Chlorophenyl)amino)-2-oxoethyl)-1-((4-chlorophenyl)sulfonyl)piperidine-3-carboxamide (9d):** Yellow solid; yield: 55%; m.p.: 168-170 ºC; IR (UATR, ν_{max}, cm^{-1}): 3314 (NH), 2957 (NH), 1492 (S=O), 1658 (C=O), 1537 (ArC=C); ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 1.40-1.56 (m, 4H), 1.57-1.62 (m, 3H), 2.0 (d 1H), 3.54 (t, 1H), 3.70 (d, 1H), 4.25 (m, 1H), 4.59 (d, 1H), 7.36 (d, *J* = 8.4 Hz, 2H), 7.631 (d, *J* = 8.4 Hz, 4H), 7.74 (d, *J* = 8.4 Hz, 2H), 8.15 (d, *J* = 7.6 Hz, 1H), 10.16 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ ppm: 28.56, 29.20, 31.32, 40, 52, 54, 121.26, 127.37, 129.14, 129.63, 137.90, 138.35, 139.04, 170.60, 171.60. MS *m/z* (%): 470.7; HPLC: 98.2%, RT: 6.54 min; Anal. calcd. (found) % for $C_{20}H_{21}Cl_2N_3O_4S$; C, 51.07 (51.01); H, 4.50 (4.43); Cl, 15.07 (15.07); N, 8.93 (8.98); O, 13.61 (13.61); S, 6.82 (6.82).

1-((4-Bromo-2-methoxyphenyl)sulfonyl)-*N*-(2-((4-chlorophenyl)amino)-2-oxoethyl)piperidine-3-carboxamide (9e): Yellow solid; yield: 67%; m.p.: 166-167 ºC; IR (UATR, ν_{max}, cm^{-1}): 3317 (NH), 2929 (NH), 1476 (S=O), 1658 (C=O), 1537 (ArC=C), 850-550 (C-Cl), 690-515 (C-Br); ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 1.45-1.51 (m, 3H), 1.51-1.621 (m, 3H), 2.0 (d 1H), 3.6-3.76 (m, 2H), 4.21-4.31 (m, 1H), 4.52 (d, 1H), 7.21 (d, *J* = 8.8 Hz, 2H), 7.36 (d, *J* = 8.8 Hz, 2H), 7.75-7.80 (m, 3H), 8.96 (d, *J* = 7.6 Hz, 1H), 10.17 (S, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ ppm: 28.18, 29.96, 41.01, 48. 46, 56.95, 59.08, 61.61, 115.95, 120.59, 125.99, 132.08, 133.83, 135.01, 136.36, 142.08, 143.11, 161.22, 167.54, 175.65, 176.38. HPLC: 94.8%, RT: 6.31 min; Anal. calcd. (found) % for $C_{21}H_{23}BrClN_3O_5S$; C, 46.29 (46.24); H, 4.25 (4.29); Br, 14.67 (14.67); Cl, 6.51 (6.51); N, 7.71 (7.77); O, 14.68 (14.68); S, 5.89 (5.89).

1-((4-Bromo-3-fluorophenyl)sulfonyl)-*N*-(2-((4-chlorophenyl)amino)-2-oxoethyl)piperidine-3carboxamide (9f): Brown solid; yield: 74%; m.p.: 182-183 ºC; IR (UATR, ν_{max}, cm^{-1}): 3313 (NH), 2929 (NH), 1491 (S=O), 1150 (S=O); 1669 (C=O), 1537 (C=C); 690-520 (C-Br), 850 (C-Cl); ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 1.45-1.59 (m, 3H), 1.65-1.70 (m, 3H), 2.0 (d 1H), 3.5 (t, 1H), 3.75 (d, 1H), 4.25 (m, 1H), 4.60 (d, 1 H), 7.36 (d, *J* = 8.8 Hz, 2H), 7.51 (d, *J* = 8 Hz, 2H), 7.61 (d, *J* = 8.8 Hz, 2H), 7.68 (d, *J* = 8 Hz, 1 H), 7.91 (t, *J* = 7.6 Hz, 1H), 8.19 (d, *J* = 7.6 Hz, 1H), 10.18 (S, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ ppm: 21.93, 23.40, 24.86, 43.32, 52.14, 54.39, 113.84, 115.58, 121.26, 124.78, 127.38, 129.08, 134.94, 138.30, 141.40, 157.16, 159.63, 170.48, 171.52. MS m/z (%): 533.1 (M+H); HPLC: 97.4%, RT: 5.34 min; Anal. calcd. (found) % for $C_{20}H_{20}BrClFN_3O_4S$; C, 45.08 (45.10); H, 3.78 (3.79); Br, 15.00 (15.01); Cl, 6.65 (6.66); F, 3.57 (3.57); N, 7.89 (7.90); O, 12.01 (12.05); S, 6.02 (6.02).

***N*-(2-((4-Chlorophenyl)amino)-2-oxoethyl)-1-((2,3-dihydro-1*H*-inden-5-yl) sulfonyl)piperidine-3-carboxamide (9g):** Off white solid; yield: 69%; m.p.: 177-178 ºC; IR (UATR, ν_{max}, cm^{-1}): 3314 (NH), 2957 (NH), 1492 (S=O), 1658 (C=O), 1537 (ArC=C), 772 (C-C); ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 1.40-1.51 (m, 3H), 1.51-1.60 (m, 3H), 2.0 (d 1H), 3.67 (d, 2H), 4.57 (d, 1H), 4.34 (m, 1H), 2.04 (t, 2H), 2.71 (t, 2H), 4.35 (d,) 4.65 (d, 1 H), 7.34 (d, *J* = 8.8 Hz, 2H), 7.58 (d, *J* = 8.8 Hz, 2H), 7.58-7.65 (m, 3H), 8.07 (d, *J* = 7.6 Hz, 1H), 10.17 (S, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ ppm: 22.57, 23.45, 32.79, 43.07, 52.3, 54.5, 122.88, 124.11, 128.25 125.34, 125.57, 125.68, 137.87, 138.35, 145.22, 149.47, 162.78, 170.79, 171.56. HPLC: 95.2%, RT: 6.66 min; Anal. calcd. (found) % for $C_{24}H_{28}ClN_3O_4S$; C, 58.83 (58.87); H, 5.76 (5.83); Cl, 7.24 (7.24); N, 8.58 (8.44); O, 13.06 (13.06); S, 6.54 (6.54).

1-((4-Nitrophenyl)sulfonyl)-*N*-(2-((4-chlorophenyl)-amino)-2-oxoethyl)piperidine-3-carboxamide (9h): Yellow solid; yield: 63%; m.p.: 184-185 ºC; FTIR (UATR, ν_{max}, cm^{-1}): 3498 (N–H), 3004 (N–H), 1684 (C=O), 1611 (Ar C=C), 1434 (S=O), 1331 (N–O), 819 (C–Cl); ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 2.00 (d, 1H), 3.19 (d, 2H), 4.35 (m, 1H), 4.58 (d, 1H), 7.00 (d, *J* = 8.8 Hz, 2H), 7.15 (d, *J* = 8.8 Hz, 2H), 7.35 (d, *J* = 8.8 Hz, 2H), 7.40 (d, *J* = 8.4 Hz, 2H), 7.41 (d, *J* = 8.4 Hz, 2H), 7.93 (d, *J* = 7.6 Hz, 1H), 10.03 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ ppm: 24.27, 28.78, 29.50, 46.15, 55.71, 58.00, 120.43, 121.30, 128.30, 129.42, 133.40, 136.34, 153.09, 157.51, 161.00, 162.13, 170.00.; MS *m/z* (%): 481.2 (M+H); HPLC: 97.4% RT: 7.12 min; Anal. calcd. (found) % for $C_{20}H_{21}ClN_4O_6S$; C, 49.95 (49.92); H, 4.40 (4.41); Cl, 7.37 (7.35); N, 11.65 (11.67); O, 19.96 (19.99); S, 6.67 (6.02).

***N*-((4-Methoxyphenyl)sulfonyl)-*N*-(2-((4-chlorophenyl)-amino)-2-oxoethyl)piperidine-3-carboxamide (9i):** Yellow solid; yield: 78%; m.p.: 146-149 ºC; FTIR (UATR, ν_{max}, cm^{-1}): 3497 (N–H), 3271 (N–H), 1696 (C=O), 1611 (Ar C=C), 1471 (S=O), 1263 (C–O), 820 (C–Cl). ^{13}C NMR (100 MHz, DMSO-d_6) δ ppm: 25.63, 25.97, 31.49, 44.78, 45.03, 46.13, 56.70, 117.76, 118.18, 119.16, 122.48, 122.73, 129.33, 136.63, 162.64, 168.26, 178.28; MS *m/z* (%): 466.1 (M+H); HPLC: 99.2 % RT: 6.11 min; Anal. calcd. (found) % for $C_{21}H_{24}ClN_3O_5S$: C, 54.13 (54.19); H, 5.19 (5.11); Cl, 7.61 (7.60); N, 9.02 (8.94); O, 17.17 (17.16); S, 6.88 (6.87).

1-((4-Methylphenyl)sulfonyl)-*N*-(2-((4-chlorophenyl)-amino)-2-oxoethyl)piperidine-3-carboxamide (9j): Brown solid; yield: 75%; m.p.: 154-155 ºC; FTIR (UATR, ν_{max}, cm^{-1}): 3410, 3091 (N–H), 1707 (C=O), 1606 (Ar C=C), 1499 (S=O), 839 (C–Cl). MS *m/z* (%): 454.1 (M+H); HPLC: 98.3 % RT: 6.44 min; Anal. calcd. (found) % for $C_{21}H_{24}ClN_3O_4S$; C, 56.00 (56.10); H, 5.38 (5.38); Cl, 7.88 (7.90); N, 9.34 (9.36); O, 14.22 (14.20); S, 7.13 (7.11).

Biological activity: All the synthesized compounds (**9a-j**) were evaluated for *in vitro* antimicrobial activity. The antibacterial activity was examined against two Gram-positive bacteria *viz*. *Staphylococcus aureus* strain (NCIM-2901) and *Bacillus subtilis* (NCIM-2063), a Gram-negative bacterium, *Escherichia*

coli (NCIM-2256) and three fungal stains *e.g*. *Candida albicans* (NCIM-3471), *Aspergillus flavus* (NCIM-539) and *Aspergillus niger* (NCIM-1196).

The antibacterial activity of the synthesized compounds was evaluated using a modified microdilution method to determine their minimum inhibitory concentration (MIC, µg/mL), minimum bacterial concentration (MBC) and minimum fungicidal concentration (MFC). For bacterial strains, MICs were determined using a serial microdilution technique with a 96-well microtiter plate reader. Compounds **9a-j** were dissolved in a saline (0.8% NaCl) solution containing 5% DMSO. All microbial strains were incubated with varying concentrations of each compound in a 96-well microtiter plate for 20 h at 37 ºC on a rotary shaker (160 rpm). The lowest concentration values that did not exhibit growth during incubation were identified as MICs.

The MIC for fungal strains was ascertained on potato dextrose agar (PDA) Medium using the agar dilution method. Following a 72 h inoculation period, compounds under investigation were dissolved in saline containing 5% DMSO and the MBC and MFC of compounds were ascertained by serial subcultivation. The mean reading served as the final reading for each experiment, was carried out in triplicate. A negative control of 5% DMSO was used, with ciprofloxacin acting as the standard antibacterial drug and fluconazole and miconazole as standard antifungal drugs.

RESULTS AND DISCUSSION

The detailed synthesis of 4-chlorophenyl)sulfonyl)piperidine-3-carboxamide (**9a-j**) involves the protection, deprotection, amide and sulfonamide coupling reactions from readily available 4-chloroaniline (**1**). The synthesized derivatives indergo electron donating and electron withdrawing substituents bearing on aromatic nuclei. To avoid expensive reagents and time consuming purifications, a simplified reaction conditions is developed for all stages and all of the synthesized compounds with high purity.

The amide coupling reaction between 4-chloroaniline and Boc-protected glycine produced intermediate **3** with an 85% yield in DMF when HATU and DIPEA were used. The reaction used EDCI, HOBt and DIPEA in DMF for amide coupling and 4 M HCl in dioxane was used to deprotect the glycine amide-coupled derivative **3**, which produced the free amine derivative with a high yield of 95%. The next step was to couple compound **4** to piperidine-3-carboxylic acid (**5**) by amide coupling in DMF using HATU and DIPEA, which produced a significant 80% yield. A different reaction procedure that used HOBt in DMF and EDCI produced a 60% yield. Compound **6** was then treated with TFA to deprotect it, resulting in a remarkable 95% reaction yield for the synthesis of compound **7**. Compound **7** was recognized as a crucial intermediate, possesses a free secondary amine connected by a piperidine that has undergone further functionalization. Using DIPEA as a base, sulfonyl chlorides (**8a-j**) were substituted for the secondary amine, leading to the synthesis of the final derivatives, which are characterized by sulfonamide coupling (**9a-j**). This multistep synthetic process, which successfully synthesizes the desired sulfonamide-coupled molecules, demonstrates how to make effective use of several coupling reagents and deprotection techniques.

To maximize yields, the optimize separation procedures and provide financial sustainability, several base and solvent combinations were investigated for the sulfonamide coupling phase. At first, pyridine in DCM was used in combination, which produced a 50% reaction yield. Due to solvent solubility concerns, other combinations were examined, such as triethylamine (TEA) in DCM, which had a 40% reaction yield. With DIPEA in DCM, the same outcomes were noted, producing a 38% response yield. To get the necessary derivatives, it was decided to employ DIPEA in DMF based on these findings. This method regularly produced yields between 70% and 90% and easy to isolate the individual components. The intended final compounds precipitated with exceptional purity after an aqueous workup.

Biological activity: The synthesized compounds exhibit notable levels of antifungal and antibacterial activity, ranging from moderate to good, following the antimicrobial results (Table-1). Compounds **9a**, **9b**, **9d** and **9h** stand out as exceptionally good and active antimicrobial agents within the series.

TABLE-1
ANTIMICROBIAL ACTIVITY DATA FOR COMPOUNDS (**9a-j**)

Compounds	MIC values[a] (µg/mL)					
	B. subtilis	*E. coli*	*S. aureus*	*C. albicans*	*A. flavus*	*A. niger*
9a	30	25	22	12.5	25	50
9b	28	28	32	12.5	25	40
9c	48	65	85	65	80	80
9d	28	32	36	25	50	40
9e	36	50	39	90	60	50
9f	33	60	60	75	70	50
9g	50	50	39	90	60	50
9h	26	29	41	12.5	50	40
9i	55	57	36	90	60	80
9j	52	67	75	75	59	80
Ciprofloxacin	26	26	25	–	–	–
Fluconazole	–	–	–	36	23	23
Miconazole	–	–	–	13.5	13.5	13.5

[a]Values are the average of three readings.

A deeper look at the antimicrobial activity data reveals that compounds **9b** and **9h** are significantly more effective than the standard, with increased activity. Compounds **9e** and **9f**, on the other hand, show a modest amount of efficacy against every tested antimicrobial strain. The synthesized compounds show a range of antibacterial characteristics overall, with several compounds in the series showing significant effectiveness against various microbial strains.

The most active compounds for Gram-negative bacteria were **9a**, **9b** and **9h**; the other compounds were either inert or moderately active. Compounds **9a**, **9b** and **9h** were successfully compared with standard for antifungal activity; the remaining compounds are primarily inert. When compared to fungal strains, derivatives of sulfonyl-2-oxoethyl piperidine-3-carboxamide exhibited more activity against antibacterial strains. The SAR can be drawn like that when piperidine-3-carboxamide is substituted with more electron donating groups the activity decreases and if electron withdrawing groups are attached then it shows better activity. In most derivatives, the activity decreases for fungal strains compared with bacterial strains. The substitution of the aromatic ring with electron-donating groups such as methoxy, *t*-butyl or fluoro significantly reduces antibacterial activity. Rings containing electron-withdrawing substitutions, such as nitro, cyano or bromo groups, exhibit an increase in relative activity. When compared to other electron-withdrawing substituents, such as cyano and halogens, compound **9h**, which contains a nitro substitution at the *para*-position, is demonstrating good activity. A similar type of results were obtained for cyano derivative compounds.

Conclusion

In conclusion, 1-((substituted-phenyl)sulfonyl)-*N*-(2-((4-chlorophenyl)amino)-2-oxoethyl)piperidine-3-carboxamide derivatives (**9a-j**) were effectively synthesized started with 4-chloroaniline (**1**). To achieve good yields and distinct reaction profiles, several meticulously regulated reactions were used. Most of the synthesized compounds had moderate to good antibacterial properties. Remarkably, an analysis contrasting molecules with substituents that donate electrons with those that extract electrons revealed that the former group had more biological activity. These findings highlight the possible importance of certain structural differences in affecting the biological characteristics of synthetic derivatives.

ACKNOWLEDGEMENTS

The authors express their gratitude to the Head of The Principal of Abeda Inamdar College, Nowrosjee Wadia College and Annasaheb Magar College, as well as Chemsar Research Centre and Aste Analytic Research Institute, for providing the essential research facilities and infrastructural support for this research endeavor. Special thanks is also owed to Savitribai Phule Pune University for assistance in recording the spectra of the compounds.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interests regarding the publication of this article.

REFERENCES

1. V.R. Pattabiraman and J.W. Bode, Nature, **480**, 471 (2011); https://doi.org/10.1038/nature10702
2. A. Trowbridge, S.M. Walton and M.J. Gaunt, *Chem. Rev.*, **120**, 2613 (2020); https://doi.org/10.1021/acs.chemrev.9b00462
3. C. Lee, H.J. Kang and S. Hong, *Chem. Sci.*, **15**, 442 (2024); https://doi.org/10.1039/D3SC05589B
4. J.R. Dunetz, J. Magano and G.A. Weisenburger, *Org. Process Res. Dev.*, **20**, 140 (2016); https://doi.org/10.1021/op500305s
5. R.M. Lanigan, P. Starkov and T.D. Sheppard, *J. Org. Chem.*, **78**, 4512 (2013); https://doi.org/10.1021/jo400509n
6. J. Wegner, S. Ceylan and A. Kirschning, *Adv. Synth. Catal.*, **354**, 17 (2012); https://doi.org/10.1002/adsc.201100584
7. S. Singh, V.J. Roy, N. Dagar, P.P. Sen and S.R. Roy, *Adv. Synth. Catal.*, **363,** 937 (2021); https://doi.org/10.1002/adsc.202001176
8. N. Armstrong and E. Gouaux, *Neuron*, **28**, 165 (2000); https://doi.org/10.1016/S0896-6273(00)00094-5
9. M.M. Joullié and K.M. Lassen, *ARKIVOC*, **2010**, 189 (2010); https://doi.org/10.3998/ark.5550190.0011.816
10. E. Massolo, M. Pirola and M. Benaglia, *Eur. J. Org. Chem.*, **2020**, 4641 (2020); https://doi.org/10.1002/ejoc.202000080
11. T. Krause, S. Baader, B. Erb and L.J. Gooßen, *Nat. Commun.*, **7**, 11732 (2016); https://doi.org/10.1038/ncomms11732
12. P. Cherkupally, S. Ramesh, B.G. de la Torre, T. Govender, H.G. Kruger and F. Albericio, *ACS Comb. Sci.*, **16**, 579 (2014); https://doi.org/10.1021/co500126y
13. C.A.G.N. Montalbetti and V. Falque, *Tetrahedron*, **61**, 10827 (2005); https://doi.org/10.1016/j.tet.2005.08.031
14. Y. Li, E. Gabriele, F. Samain, N. Favalli, F. Sladojevich, J. Scheuermann and D. Neri, *ACS Comb. Sci.*, **18**, 438 (2016); https://doi.org/10.1021/acscombsci.6b00058
15. P.E. Bunney, A.N. Zink, A.A. Holm, C.J. Billington and C.M. Kotz, *Physiol. Behav.*, **176**, 139 (2017); https://doi.org/10.1016/j.physbeh.2017.03.040
16. J. Pícha, M. Budìšínský, I. Hanèlová, M. Šanda, P. Fiedler, V. Vanìk and J. Jiráèek, *Tetrahedron*, **65**, 6090 (2009); https://doi.org/10.1016/j.tet.2009.05.051
17. A. Torvisco, A.Y. O'Brien and K. Ruhlandt-Senge, *Coord. Chem. Rev.*, **255**, 1268 (2011); https://doi.org/10.1016/j.ccr.2011.02.015
18. R. Aslanian, J.J. Piwinski, X. Zhu, T. Priestley, S. Sorota, X.-Y. Du, X.-S. Zhang, R.L. McLeod, R.E. West, S.M. Williams and J.A. Hey, *Bioorg. Med. Chem. Lett.*, **19**, 5043 (2009); https://doi.org/10.1016/j.bmcl.2009.07.047
19. D. Procopio, C. Siciliano and M.L. Di Gioia, *Org. Biomol. Chem.*, **22**, 1400 (2024); https://doi.org/10.1039/D3OB01673K
20. P.J. Czerwiński and B. Furman, *Front. Chem.*, **9**, 655849 (2021); https://doi.org/10.3389/fchem.2021.655849
21. J. Sienkiewicz-Gromiuk and A. Drzewiecka-Antonik, *Molecules*, **27**, 8203 (2022); https://doi.org/10.3390/molecules27238203
22. J. Du, J. Guo, D. Kang, Z. Li, G. Wang, J. Wu, Z. Zhang, H. Fang, X. Hou, Z. Huang, G. Li, X. Lu, X. Liu, L. Ouyang, L. Rao, P. Zhan, X. Zhang and Y. Zhang, *Chin. Chem. Lett.*, **31**, 1695 (2020); https://doi.org/10.1016/j.cclet.2020.03.028
23. I. Khan, S. Zaib, S. Batool, N. Abbas, Z. Ashraf, J. Iqbal and A. Saeed, *Bioorg. Med. Chem.*, **24**, 2361 (2016); https://doi.org/10.1016/j.bmc.2016.03.031
24. K. R. Campos, P.J. Coleman, J.C. Alvarez, S.D. Dreher, R.M. Garbaccio, N.K. Terrett, R.D. Tillyer, M.D. Truppo and E.R. Parmee, *Science*, **363**, eaat0805 (2019); https://doi.org/10.1126/science.aat0805

25. G. Wu, T. Zhao, D. Kang, J. Zhang, Y. Song, V. Namasivayam, J. Kongsted, C. Pannecouque, E. De Clercq, V. Poongavanam, X. Liu and P. Zhan, *J. Med. Chem.*, **62**, 9375 (2019); https://doi.org/10.1021/acs.jmedchem.9b00359
26. J. Xie, Z.-Q. Long, A.-Q. Chen, Y.-G. Ding, S.-T. Liu, X. Zhou, L.-W. Liu and S. Yang, *Int. J. Mol. Sci.*, **24**, 5861 (2023); https://doi.org/10.3390/ijms24065861
27. Y. Yang, K. Chen, G. Wang, H. Liu, L. Shao, X. Zhou, L. Liu and S. Yang, *Int. J. Mol. Sci.*, **24**, 10566 (2023); https://doi.org/10.3390/ijms241310566
28. N.A. Mohsin and M. Ahmad, *Braz. J. Pharm. Sci.*, **56**, e18325 (2020); https://doi.org/10.1590/s2175-97902019000418325
29. F. Wang, B.-X. Yang, T.-H. Zhang, Q.-Q. Tao, X. Zhou, P.-Y. Wang and S. Yang, *Arab. J. Chem.*, **16**, 104479 (2023); https://doi.org/10.1016/j.arabjc.2022.104479
30. L. Zhang, X.M. Peng, G.L.V. Damu, R.X. Geng and C.H. Zhou, *Med. Res. Rev.*, **34**, 340 (2014); https://doi.org/10.1002/med.21290
31. C. -H. Zhou and Y. Wang, *Curr. Med. Chem.*, **19**, 239 (2012); https://doi.org/10.2174/092986712803414213
32. R.J. Obaid, N. Naeem, E.U. Mughal, M.M. Al-Rooqi, A. Sadiq, R.S. Jassas, Z. Moussa and S.A. Ahmed, *RSC Adv.*, **12**, 19764 (2022); https://doi.org/10.1039/D2RA03081K
33. K. Biernacki, M. Dasko, O. Ciupak, K. Kubiñski, J. Rachon and S. Demkowicz, *Pharmaceuticals*, **13**, 111 (2020); https://doi.org/10.3390/ph13060111
34. M.S.A. El-Gaby, Y.A. Ammar, M.I.H. El-Qaliei, A.M. Ali, M.F. Hussein and F.A. Faraghally, *Egypt. J. Chem.*, **63**, 5289 (2020); https://doi.org/10.21608/EJCHEM.2020.33860.2707
35. S. Mohammed, A. AL-Hadedi and S. Abood, *Rafidain J. Sci.*, **31**, 64 (2022); https://doi.org/10.33899/rjs.2022.175395
36. C.T. Supuran, A. Casini and A. Scozzafava, *Med. Res. Rev.*, **23**, 535 (2003); https://doi.org/10.1002/med.10047
37. F. Carta, A. Scozzafava and C.T. Supuran, *Expert Opin. Ther. Pat.*, **22**, 747 (2012); https://doi.org/10.1517/13543776.2012.698264
38. A. Ali, P. Hasan, M. Irfan, A. Uddin, A. Khan, J. Saraswat, R. Maguire, K. Kavanagh, R. Patel, M.C. Joshi, A. Azam, M. Mohsin, Q.M.R. Haque and M. Abid, *ACS Omega*, **6**, 27798 (2021); https://doi.org/10.1021/acsomega.1c03379
39. S. Of, *Novel Res. Strategies Sulfonamide*, **9**, 2623 (2020).
40. S. Kumar Verma, R. Verma, F. Xue, P. Kumar Thakur, Y.R. Girish and K.P. Rakesh, *Bioorg. Chem.*, **105**, 104400 (2020); https://doi.org/10.1016/j.bioorg.2020.104400
41. A.M.G. Pinto, Ph.D. Thesis, Common Scaffolds for the Enantioselective Synthesis of Marine, Plant, and Amphibian *cis*-Decahydroquinoline Alkaloids, Faculty of Pharmacy and Food Sciences, Department of Pharmacology, Toxicology and Therapeutic Chemistry, University of Barcelona, Barcelona, Spain(2017).
42. G.Z. Papadakis and C. Millo, *Physiol. Behav.*, **176**, 139 (2011).
43. K.K. Li, C. Luo, D. Wang, H. Jiang and Y.G. Zheng, *Med. Res. Rev.*, **32**, 815 (2012); https://doi.org/10.1002/mrr.20228
44. K.C. Nicolaou, P.G. Bulger and D. Sarlah, *Angew. Chem. Int. Ed.*, **44**, 4490 (2005); https://doi.org/10.1002/anie.200500369
45. P. Jones, K. Wilcoxen, M. Rowley and C. Toniatti, *J. Med. Chem.*, **58**, 3302 (2015); https://doi.org/10.1021/jm5018237
46. M.M. Abdelshaheed, I.M. Fawzy, H.I. El-Subbagh and K.M. Youssef, *Future J. Pharm. Sci.*, **7**, 188 (2021); https://doi.org/10.1186/s43094-021-00335-y
47. E. Martini, C. Ghelardini, L. Guandalini, D. Manetti, M. Melchiorre, S. Dei, M. Norcini, S. Scapecchi, E. Teodori and M.N. Romanelli, *Bioorg. Med. Chem.*, **16**, 1431 (2008); https://doi.org/10.1016/j.bmc.2007.10.050
48. M.K. Prashanth, H.D. Revanasiddappa, K.M. Lokanatha Rai and B. Veeresh, *Bioorg. Med. Chem. Lett.*, **22**, 7065 (2012); https://doi.org/10.1016/j.bmcl.2012.09.089
49. P.M. Weintraub, J.S. Sabol, J.M. Kane and D.R. Borcherding, *Tetrahedron*, **59**, 2953 (2003); https://doi.org/10.1016/S0040-4020(03)00295-3
50. J.M. Kamenka, B. Chiche, R. Goudal, P. Geneste, J. Vignon, J.P. Vincent and M. Lazdunski, *J. Med. Chem.*, **25**, 431 (1982); https://doi.org/10.1021/jm00346a019