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Research Article

SYNTHESIS AND BIOLOGICAL SCREENING OF NEW AZASPIRO [2, 4] HEPTANECARBOXYLATE DERIVATIVES

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ABSTRACT

Spiro ring molecules including their derivatives are found to be handy intermediates in the fusion of medicinally active molecules. In recent years due to many interesting biological activity applications associated ample attention by the researchers has been given to spiro compound. Many spiro compounds contain nitrogen. The work aims at ground work of methyl- 5-(1-4- substituted phenyl ethyl)-5-azaspiro [2, 4] heptane-6-carboxylate react with methyl [({1-[acetyloxy) methyl] cyclopropyl} methyl) (1-phenylethyl) amino] acetate along with NaH and toluene to find out most favorable reaction conditions and additional study of its properties. The synthesized compounds were characterized by ^{1}H NMR; C^{13} NMR was dogged in $CDCl_3$/dimethyl sulfoxide solution on a Bruker Ac 400 MHz spectrometer.

Keywords: Azaspiro Compounds, Methyl-5-(1-sustituted phenyl ethyl)-5-azaspiro [2, 4] heptane-6-carboxylate

1. INTRODUCTION

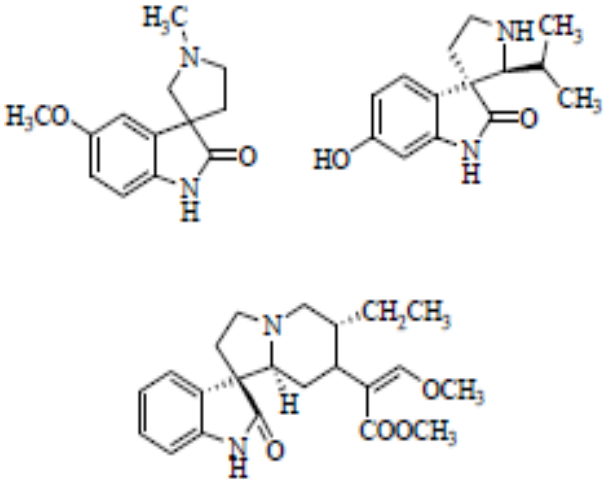
Spiro ring molecules including their derivatives are found to be handy intermediates in the fusion of medicinally active molecules. In recent years due to many interesting biological activity applications associated, a very good attention by the researchers has been given to spiro compound. Spiro cyclic compound have enchanted research since past few decades among different trends in drug design, the introduction of fluorine-containing substituent's proved to be one of the most useful [1], and the use of nonaromatic, 3D-shaped building blocks is one of the most recent approaches [2]. However, efforts to minimize toxicity, often associated with the presence of aromatic and heteroaromatic moieties, as well as the requirement for novelty and patentability have eventually led to an increase in the interest toward conformationally restricted, and nonaromatic building blocks [3-5]. They were found to be active molecules to possess antimicrobial, antileukaemic, anticonvulsant, anesthetic etc. activities. For example Azaspiro[3.3]heptane derivatives have been often considered as conformationally restricted analogues of piperidine with unique properties.

Modern drug discovery has been changing rapidly with terms like scaffold hoppingm[6], escape flat land [7]. In this context chemists are currently looking for novel 3D-shaped Fsp3-rich building blocks [8].

In 2010, Müller and Carreira demonstrated the high potential of azaspirocycles as building blocks for drug discovery [10].

Many Spiro compound containing nitrogen i.e. Spiro heterocycles have been discovered to play chief role in physiological processes and have demonstrated noteworthy pharmacological activities. Indeed 2,6-diazaspiro[3.3]heptanes have recently drawn significant interest in the pharmaceutical industry as a structural surrogate for the piperazine ring system [11]. Whereas 2,6 diazaspiro[3.3]heptanes have been known since the 1930s [12] and have been the subject of significant interest in the synthetic community [13].Few examples include spiro [pyrrolidineoxindole] alkaloids such as elacomine, horsfiline and rhynchophylline.

The work aims at groundwork of methyl-5-(1-4-substituted phenyl ethyl)-5-azaspiro [2, 4] heptane-6-carboxylate react with methyl [({1-[acetyloxy) methyl] cyclopropyl} methyl) (1- phenylethyl) amino] acetate along with NaH and toluene to find out most favorable reaction conditions and additional study of its properties by exploring the literature as mentioned above. Some other experiments were also done in our laboratory [14-20].

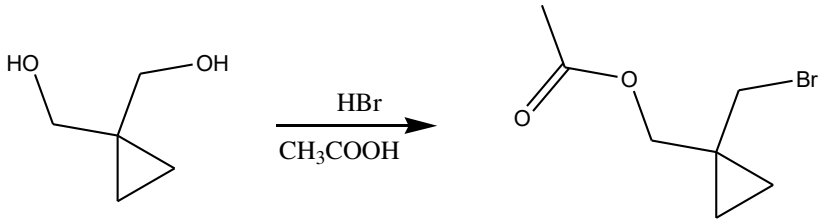


2. MATERIAL AND METHODS

An open capillary tubes method and uncorrected m.p. were reported. Pattern of the compound was on the whole tartan by TLC on silica gel plates (0.51 mm) thickness and stains were situated by Ultra Violate. Infrared spectra were documentation in Shimadzu instrument FTIR-8400 using KBr method. MS were recorded on Shimadzu GC-MS-QP-2010 mold using express Injection probe method and Turbo spray model using chemical isolation technique. ^{1}H NMR was dogged in $CDCl_3$ / dimethyl sulfoxide solution on a Bruker Ac 400 MHz spectrometer.

2.1. Synthesis of [1-(bromo methyl) cyclopropyl] methyl acetate

Added 1, 1-cyclopropyl methanol in dichloromethane and cooled the mixture to 0°C- 5°C. Slowly added Hydrogen Bromide in CH_3COOH in to the mass at below 20°C. After addition the mass was stirred at 15°C-20°C for 1 hr followed by stirring at 21°C-25°C for 2 hr. The reaction progress was checked by Thin Layer Chromatography. After completion the reaction mass was dumped into cold water and stirred for 30 min. The organic layer was separated and given back extracted by dichloromethane to aqueous layer. Combined organic layer added into water and adjusted pH 6-7 by 15 % sodium hydroxide solution. The organic layer was separated and dried by sodium sulphate. The organic layer was concentrated to obtain [1-(bromomethyl) cyclopropyl] Methyl acetate.

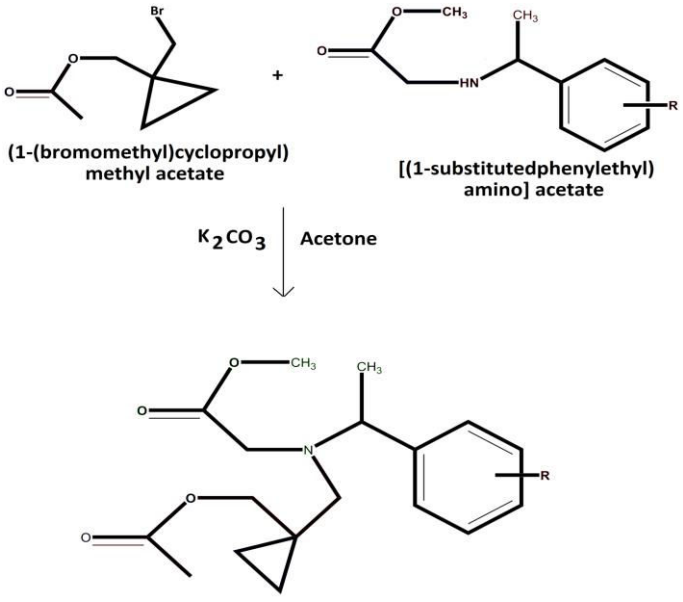


1,-cyclopropyl demethanol

(1-(bromomethyl)cyclopropyl) methyl acetate

2.2. Preparation of Methyl [({1-[acetyloxy) methyl] cyclopropyl} methyl) (1-phenylethyl) amino] acetate

Added [1-(bromomethyl)cyclopropyl] methyl acetate in to 100 mL acetone followed by addition of 8.6 g of potassium carbonate and methyl [(1-phenylethyl)amino]acetate at 20°C-30°C. Stirred the reaction mass at 25°C-35°C for 15 hrs. Reaction progress was monitored by TLC. After completion of the reaction, the reaction mass was filtered and washed with 50 mL distilled acetone added dichloromethane. The organic layer aws washed with awter and the organic layer was concentrated to obtain methyl [({1-[acetyloxy) methyl] cyclopropyl}methyl)(1-phenylethyl)amino]acetate.



(1-(bromomethyl)cyclopropyl) methyl acetate

[(1-substitutedphenylethyl) amino] acetate

2.3. General procedure for the synthesis of methyl-5-(1-sustituted phenyl ethyl)-5 azaspiro [2, 4] heptane-6-carboxylate (VK- 301 to 310)

Added methyl [({1-[acetyloxy) methyl] cyclopropyl} methyl) (1-phenyl ethyl) amino] acetate in toluene followed by addition of sodium hydride at 20°C to 30°C in stepwise manner. Mixture was heated to 70°C for 5 hrs. The reaction progress was checked by Thin Layer Chromatography. Upon completion, the reaction mass was dumped in cooled water and stirred for 30 min followed by washing with toluene. Toluene distilled methyl-5-(1-phenylethyl)-5-azaspiro [2, 4] heptane-6-carboxylate was collected.

2.4. Antimicrobial Evaluation

Antimicrobial efficiency of test compounds in terms of minimum inhibitory conc. (MIC) *i.e.* the minimum concentration that can effectively inhibits bacteria, was determined.

Synthesized compounds (VK-301 to 310) were checked for their antibacterial and anti-fungal activity *in vitro* by dilution probe method [3-5] with 2 Gram +Ve bacteria *i.e. Staphylococcus aureus* (MTCC-96), *Streptococcus pyogenes* (MTCC 443), 2 Gram-Ve bacteria i.e. *Escherichia coli* (MTCC 442), *Pseudomonas aeruginosa* (MTCC 441) and 3 fungal strains i.e. *Candida albicans* (MTCC 227), *Aspergillus Niger* (MTCC 282) and *Aspergillus clavatus* (MTCC 1323) taking ampicillin, gentamicin, ciprofloxacin, chloramphenicol, nystatin, norfloxacin and griseofulvin as standard drugs. The standard strains were procured from the MTCC, Institute of Microbial Technology, Chandigarh, India.

3. RESULTS AND DISCUSSION

The structure of synthesized compounds was established on the basis of FTIR, ^{13}CNMR & ^{1}H NMR and Mass spectral data. All the title compounds showed a characteristic adsorption bands between 2950-3100 cm^{-1} (Aromatic symmetrical stretch of C-H), 2930-2960 (C-H asymmetrical stretch of CH3 group), 1661-1710 (C=O stretch of ester), around 1591 and 1522 (Aromatic ring, C=C stretch), 1195 (C-N stretch), 1070-1110 (Aromatic ring, C-H in plane deformation), 750-790 (C-H out of plane deformation of mono substituted benzene ring).

It can be concluded that method used for synthesis of ingenious methyl-5-(1-4-substituted phenyl ethyl)-5-azaspiro [2, 4] heptane-6-carboxylate was good which produces good yields between 53% to 66% by simple workup.

3.1. Spectral characteristics of synthesized compouds

3.1.1. Methyl-5-(1-phenylethyl)-5-azaspiro [2, 4] heptane-6-carboxylate (VK-301)

Yield: 60%; MP:173 °C; MS: *m/z* 259, IR (cm^{-1}): 3100 (Aromatic symmetrical stretch of C-H), 2932 (C-H asymmetrical stretch of CH3 group), 2838 (C-H asymmetrical stretch of CH_3 group), 1661 (C=O stretch of ester), 1591 and 1522 (Aromatic ring, C=C stretch), 1472 (C-H asymmetrical deformation of CH_3 group), 1342 (C-H symmetrical deformation of CH_3 group), 1244 (C-O-C asymmetrical stretch of O-CH_3), 1195 (C-N stretch), 1072 (Aromatic ring, C-H in plane deformation), 786 (C-H out of plane deformation of mono substituted benzene ring); ^{1}H NMR: 0.34-0.38 (t 2H), 0.43-0.52 (t 2H), 1.25-1.27 (s 3H), 1.30-1.33 (s 2H), 2.50-2.53 (d 2H), 3.53-3.55 (s 3H), 3.89-3.92 (t 1H) 4.05 (s 1H), 7.19-7.22 (t 1H), 7.27-7.30 (t 2H), 7.36-7.38 (dd 2H); ^{13}C NMR: 171.6, 137.4, 128.9, 128.5, 127.3, 65.0, 61.0, 56.7, 51.9, 50.9, 19.9, 19.4, 9.0.

3.1.2. Methyl-5-(1-3-bromophenylethyl)-5-azaspiro [2, 4] heptane-6-carboxylate (VK-302)

Yield: 53.6%; MP:177 °C; Mass: *m /z* 338, Infrared (cm^{-1}): 3051 (Aromatic symmetrical stretch of C-H), 2956 (C-H asymmetrical stretch of CH_3 group), 2834 (C-H asymmetrical stretch of CH_3 group),1703 (C=O stretch of ester), 1597 and 1566 (Aromatic ring, C=C stretch), 1482 (C-H asymmetrical deformation of CH_3 group), 1357 (C-H symmetrical deformation of CH_3 group), 1280 (C-O-C asymmetrical stretch of O-CH_3), 1255 (C-N stretch), 1091 (Aromatic ring, C-H in plane deformation), 742 (C-H out of plane deformation of mono substituted benzene ring), 690 (C-Br stretch); ^{1}H NMR: 0.27(t 2H), 1.38(d 3H), 1.99-1.74 (d 2H), 2.22-2.12(s2H), 3.08 (t1H), 3.67 (s3H), 4.08 (q1H), 7.06 (d1H), 7.10 (t1H), 7.25 (d1H), 7.25 (d1H), 7.29 (t 1H); ^{13}C NMR 171.6, 139.6, 133.6, 130.6, 127.9, 122.8, 65.0, 60.7, 56.7, 51.9, 50.9,19.9, 19.4, 9.0.

3.1.3. Methyl-5-(1-4-bromophenylethyl)-5-azaspiro [2, 4] heptane-6-carboxylate (VK-303)

Yield: 54.2%; MP: 169 °C; Mass: *m /z* 338; IR (cm^{-1}): 2958 (Aromatic symmetrical stretch of C-H), 2931 (C-H asymmetrical stretch of CH_3 group), 2870 (C-H

asymmetrical stretch of CH_3 group),1678 (C=O stretch of ester), 1583 and 1553 (Aromatic ring, C=C stretch), 1452 (C-H asymmetrical deformation of CH_3 group), 1383 (C-H symmetrical deformation of CH_3 group), 1253 (C-O-C asymmetrical stretch of O-CH_3), 1213 (C-N stretch), 1107 (Aromatic ring, C-H in plane deformation), 755 (C-H out of plane deformation of mono substituted benzene ring), 732(C-Br stretch); ^{1}H NMR:0.27 (t 2H),1.38 (d 3H), 1.99-1.74 (d 2H), 2.22-2.12 (s 2H), 3.08 (t 1H), 3.67 (s 3H), 4.08 (q 1H), 7.01 (d 2H), 7.38(d 2H); ^{13}C NMR 171.6,136.4,131.1,121.6, 65.0, 61.1, 56.7, 51.9, 50.9, 19.4, 9.0.

3.1.4. Methyl-5-(1-3-chlorophenylethyl)-5-azaspiro [2, 4] heptane-6-carboxylate (VK-304)

Yield: 57.2%; MP: 179 °C; Mass: *m /z* 294; Infrared (cm^{-1}): 3051 (Aromatic symmetrical stretch of C-H), 2984 (C-H asymmetrical stretch of CH_3 group), 2834 (C-H asymmetrical stretch of CH_3 group),1683 (C=O stretch of ester), 1565 and 1546 (Aromatic ring, C=C stretch), 1482 (C-H asymmetrical deformation of CH_3 group), 1357 (C-H symmetrical deformation of CH_3 group), 1255 (C-O-C asymmetrical stretch of O-CH_3), 1219 (C-N stretch), 1091 (Aromatic ring, C-H in plane deformation), 752 (C-H out of plane deformation of mono substituted benzene ring), 690(C-Cl stretch); ^{1}H NMR:0.27 (t 2H), 1.38 (d 3H), 1.99-1.74 (d 2H), 2.22-2.12 (s 2H), 3.08 (t 1H), 3.67 (s 3H), 4.08 (q 1H), 7.00 (d 1H), 7.09 (d 1H), 7.13 (t 1H), 7.15 (t 1H): ^{13}C NMR:171.6, 138.8, 134.0, 129.9, 128.7, 127.0, 65.0, 60.9, 56.7, 51.9, 50.9, 19.9, 19.4, 9.0.

3.1.5. Methyl-5-(1-4-chlorophenylethyl)-5-azaspiro [2, 4] heptane-6-carboxylate (VK-305)

Yield: 57%; MP: 178 °C; MS: *m/z* 294; IR (cm^{-1}): 3111 (Aromatic symmetrical stretch of C-H), 3074 (C-H asymmetrical stretch of Me group), 2963 (C-H asymmetrical stretch of CH_3 group), 1649 (C=O stretch of ester), 1607 and 1573 (Aromatic ring, C=C stretch), 1481 (C-H asymmetrical deformation of CH_3 group), 1349 (C-H symmetrical deformation of CH_3 group), 1251 (C-O-C asymmetrical stretch of O-CH_3), 1220 (C-N stretch), 1051 (Aromatic ring, C-H in plane deformation), 758 (C-H out of plane deformation of mono substituted benzene ring), 656 (C-Cl stretch); ^{1}H NMR: 0.27 (t 2H), 1.38 (d 3H), 1.99-1.74 (d 2H), 2.22-2.12 (s 2H), 3.08 (t 1H), 3.67 (s 3H), 4.08 (q 1H), 7.06 (d 2H), 7.22 (d, 2H); ^{13}C NMR: 171.6, 135.5, 132.8, 130.3, 128.6,65.0, 61.1, 56.7, 51.9, 50.9, 19.9, 19.4, 9.0.

3.1.6. Methyl-5-(1-4-Methylphenylethyl)-5-azaspiro [2, 4] heptane-6-carboxylate (VK-306)

Yield: 66%; MP: 182 °C; MS: *m/z* 273; IR (cm^{-1}): 3100 (Aromatic symmetrical stretch of C-H), 2958 (C-H asymmetrical stretch of CH_3 group), 2870 (C-H asymmetrical stretch of CH_3 group), 1700 (C=O stretch of ester), 1583 and 1535 (Aromatic ring, C=C stretch), 1453 (C- H asymmetrical deformation of CH_3 group), 1383 (C-H symmetrical deformation of CH_3 group), 1283 (C-O-C asymmetrical stretch of O-CH_3), 1213 (C-N stretch), 1083 (Aromatic ring, C-H in plane deformation), 758 (C-H out of plane deformation of mono substituted benzene ring); ^{1}H NMR:0.27 (t 2H), 1.38 (d 3H), 1.99-1.74 (d 2H), 2.22-2.12 (s 2H), 2.35 (s 3H), 3.08 (t 1H), 3.67(s 3H), 4.08(q 1H), 7.00 (d 2H), 7.01(d,2H); ^{13}C NMR 171.6, 136.9, 134.4, 128.6, 65.0, 61.1, 56.7, 51.9, 50.9, 24.3, 19.9, 19.4, 9.0.

3.1.7. **Methyl-5-(1-4-methoxyphenylethyl)-5-azaspiro[2, 4]heptane-6-carboxylate (VK-307)**

Yield: 53%; MP: 170 °C; MS: *m/z* 289; IR (cm^{-1}): 3118 (Aromatic symmetrical stretch of C-H), 2990 (C-H asymmetrical stretch of CH_3 group), 2870 (C-H asymmetrical stretch of CH_3 group), 1700 (C=O stretch of ester), 1561 and 1533 (Aromatic ring, C==C stretch), 1451 (C-H asymmetrical deformation of CH_3 group), 1352 (C-H symmetrical deformation of CH_3 group), 1249 (C-O-C asymmetrical stretch of O- CH_3), 1149 (C-N stretch), 1070 (Aromatic ring, C-H in plane deformation), 755 (C-H out of plane deformation of mono substituted benzene ring); ^{1}H NMR:0.27 (t 2H), 1.38 (d 3H), 1.99-1.74 (d 2H), 2.22-2.12 (s 2H), 3.08 (t 1H), 3.67 (s 3H), 3.73 (s 3H), 4.08 (q 1H), 6.72 (d 2H), 7.01 (d, 2H); ^{13}C NMR: 171.6, 159.2, 129.9, 114.0, 65.0, 61.1, 56.7, 55.9, 51.9, 50.9, 19.9, 19.4, 9.0.

3.1.8. **Methyl-5-(1-4-hydroxyphenylethyl)-5-azaspiro [2, 4] heptane-6-carboxylate (VK-308)**

Yield: 60%; MP: 173°C; MS: *m/z* 275; IR (cm^{-1}): 3118 (Aromatic symmetrical stretch of C-H), 2951 (C-H asymmetrical stretch of CH_3 group), 2831 (C-H asymmetrical stretch of CH_3 group), 1591 (C=O stretch of ester), 1545 and 1508 (Aromatic ring, C=C stretch), 1469 (C-H

asymmetrical deformation of CH_3 group), 1357 (C-H symmetrical deformation of CH_3 group), 1248 (C-O-C asymmetrical stretch of O- CH_3), 1118 (C-N stretch), 1041 (Aromatic ring, C-H in plane deformation), 745 (C-H out of plane deformation of mono substituted benzene ring); ^{1}H NMR: 0.27 (t 2H), 1.38 (d 3H), 1.99-1.74 (d 2H), 2.22-2.12 (s 2H), 3.08 (t 1H), 3.67(s 3H), 4.08 (q 1H), 5.00 (s,1H), 6.68 (d2H), 6.95 (d,2H): ^{13}C NMR 171.6, 157.0, 130.3, 130.0, 115.6, 65.0, 61.1, 56.7, 51.9, 50.9, 19.9, 19.4, 9.0.

3.1.9. Methyl-5-(1-4-nitrophenylethyl)-5-azaspiro [2, 4] heptane-6-carboxylate (VK-309)

Yield: 55%; MP: 180 ºC; MS: *m/z* 304; IR (cm^{-1}): 3100 (Aromatic symmetrical stretch of C-H), 2932 (C-H asymmetrical stretch of CH_3 group), 2838 (C-H asymmetrical stretch of CH_3 group),1661 (C=O stretch of ester), 1591 and 1522 (Aromatic ring, C=C stretch), 1550 and 1365 (C- NO2) stretch), 1472 (C-H asymmetrical deformation of CH_3 group), 1342 (C-H symmetrical deformation of CH_3 group), 1244 (C-O-C asymmetrical stretch of O- CH_3), 1195 (C- N stretch), 1072 (Aromatic ring, C-H in plane deformation), 786 (C-H out of plane deformation of mono substituted benzene ring); ^{1}H NMR: 0.27 (t 2H), 1.38 (d 3H), 1.99-1.74 (d 2H), 2.22-2.12 (s 2H), 3.08 (t 1H), 3.67 (s 3H), 4.08 (q 1H), 7.38 (d 2H), 8.14 (d,2H); ^{13}C NMR: 171.6, 146.9, 143.5, 129.8, 120.8, 65.0, 61.1, 56.7, 51.9, 50.9, 19.9, 19.4, 9.0.

3.1.10. Methyl-5-(1-4-fluorophenylethyl)-5-azaspiro [2, 4] heptane-6-carboxylate (VK-310)

Yield: 51%; MP: 178 ºC; MS: *m/z* 277; IR (cm^{-1}): 3100 (Aromatic symmetrical stretch of C-H), 2932 (C-H asymmetrical stretch of CH_3 group), 2838 (C-H asymmetrical stretch of CH_3 group),1661 (C=O stretch of ester), 1591 and 1522 (Aromatic ring, C=C stretch), 1472 (C-H asymmetrical deformation of CH_3 group),1350 (C-F stretch), 1342 (C-H symmetrical deformation of CH_3 group), 1244 (C-O-C asymmetrical stretch of O-CH3), 1195 (C-N stretch), 1072(Aromatic ring, C-H in plane deformation), 786(C-H out of plane deformation of mono substituted benzene ring); ^{1}H NMR:0.27 (t 2H), 1.38 (d 3H), 1.99-1.74 (d 2H), 2.22-2.12 (s 2H), 3.08 (t 1H), 3.67 (s 3H), 4.0 8(q 1H), 6.92 (d 2H), 7.10 (d, 2H); ^{13}C NMR: 171.6, 161.4, 133.0, 130.5, 115.2, 65.0, 61.1, 56.7, 51.9, 50.9, 19.9, 19.4, 9.0.

3.2. Antimicrobial Evaluation

The purified products were very clean. This study gives valuable synthesis of potentially biologically active compounds. All the synthesized compounds were tested for their impact on mentioned microbes.

Table: 1: Antimicrobial activity of synthesized compounds

Code	Minimal inhibition concentration (μg mL^{-1})						
	Gram-positive		Gram-negative		Fungal species		
	S. aureus	*S. pyogenes*	*E. coli*	*P. aeruginosa*	*C. albicans*	*A. Niger*	*A. clavatus*
VK-301	250	250	450	>1000	250	300	350
VK-302	400	200	>1000	350	550	350	350
VK-303	450	250	350	350	350	350	250
VK-304	100	350	200	200	350	200	300
VK-305	200	>1000	350	200	250	>1000	450
VK-306	300	350	200	350	350	250	>1000
VK-307	400	350	250	350	350	350	400
VK-308	150	200	350	250	250	450	450
VK-309	350	350	200	200	200	450	300
VK-310	100	200	100	150	>1000	350	300
Gentamycin	0.25	0.5	0.05	1	-	-	-
Ampicillin	250	100	100	100	-	-	-
Chloramphenicol	50	50	50	50	-	-	-
Ciprofloxacin	50	50	25	25	-	-	-
Norfloxacin	10	10	10	10	-	-	-
Nystatin	-	-	-	-	100	100	100
Griseofulvin	-	-	-	-	500	100	100

Broth dilution methods have been used to determine the minimal concentration of antimicrobial agent that inhibits the growth or kill the microorganisms. Detailed interpretation of results for antimicrobial evaluation is described in the table.

The result of the antimicrobial and antibacterial analyses of the synthesized compounds suggests that some of the compound shows potent activity towards the microbes and bacteria. For example, synthesized compound (VK-301) and compound (VK-302) shows good activity of >1000 MIC against gram negative *Pseudomonas aeruginosa* and *Escherichia coli* respectively. Other compounds such as (VK-305, VK-306, VK-310) shows activity >1000 MIC against antifungal strains *Aspergillus Niger, Aspergillus clavatus* and *Candida albicans* respectively. (VK-305) also shows potent activity against gram positive bacteria *Streptococcus pyogenes.*

4. CONCLUSION

We include that synthesized of ingenious methyl-51-(1-4-substituted phenylethyl)-5- azaspiro [2, 4] heptane-6-carboxylate using good method. This process produces good yields and simple workup. The purified products are very clean. This study gives valuable synthesis of potentially biologically active. The synthesized compounds VK 302, VK 305, VK306, VK310 are potentially shows good antimicrobial and antifungal activity.

5. ACKNOWLEDGEMENTS

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6. REFERENCES

1. Hagmann WK. *J. Med. Chem.,* 2008; **51:** 4359.
2. Mann A. In *The Practice of Medicinal Chemistry*; Wermuth, C. G., Ed.; Elsevier: Amsterdam, 2008, 3rd ed., 363-379.
3. Marson CM. *Chem. Soc. Rev.,* 2011; **40:**5514.
4. Hu XG, Hunter L. *Beilstein J. Org. Chem.,* 2013; **9:**2696.
5. Lovering F. *Med. Chem. Commun.,* 2013; **4:**515.
6. Böhm HJ, Flohr A, Stahl M. *Drug Discov. Today: Technologies*, 2004; **1:**217.
7. Lovering F, Bikker J, Humblet C. *J. Med. Chem*. 2009; 52:6752.
8. ***(a)*** Druzhenko T, Denisenko O, Kheylik Y, Zozulya S, Shishkina S, Tolmachev A, Mykhailiuk PK. *Org. Lett.,* 2015; 17: 1922. ***(b)*** Denisenko AV, Mityuk AP, Grygorenko OO, Volochnyuk DM, Shishkin OV, Tolmachev AA, Mykhailiuk PK.*Org. Lett.,* 2010; 12:4372.
9. Burkhard JA, Wagner B, Fischer H, Schuler F, Müller K, Carreira Angew EM.*Chem. Int. Ed.* 2010; **49:**3524.
10. Guérot C, Tchitchanov BH, Knust H, Carreira EM. *Org. Lett.,* 2011; 13:780.
11. ***(a)*** Engel W, Eberlein W, Trummlitz G, Mihm G, Doods H, Mayer N, De Jonge, *Eur. Patent*, EP 417631 1991. ***(b)*** Jones P, Kinzel O, Llauger Bufi L, Muraglia E, Pescatore G, Torrisi C. WO2007/138355 2007. ***(c)*** Bhattacharjee A, Yanming D, Duffy EM, Job G, E, Lou R, Lou Z, O'Dowd H, Tang Y, Wu Y. WO2008/106224 2008. ***(d)*** Stanton MG, Noucti N, Sloman DJ, Munoz B, Lim J. WO2009/014620 2009.
12. ***(a)*** Govaert F. *J. Proc. Acad. Sci*. Amsterdam, 1934: **37:**156. ***(b)*** Litherland A, Mann FG. *J. Chem. Soc.,* 1938; 1588.
13. ***(a)*** Hillier MC, Chen CY. *J. Org. Chem*. 2006; **71:** 7885. ***(b)*** Hamza D, Stocks MJ, De′cor A, Pairaudeau G, Stonehouse JP. *Synlett,* **2007:**2584. ***(c)*** Stocks MJ, Hamza D, Pairaudeau G, Stonehouse JP, Thorne PV. *Synlett,* 2007; 2587. ***(d)*** Burkhard J, Carreira EM. *Org. Lett*., 2008; **10:**3525.
14. Joshi KA, Makwana NR. *International Journal for Innovative Research in Multidisciplinary Field,* 2019; **7:** 16-21.
15. Joshi VN, Joshi KA, Modhavadiya VA. *European Journal of Biomedical and Pharmaceutical Sciences,* 2017; **4(12):**374-377.
16. Joshi KA, Ram HK. *International Journal of Applied Chemistry,* 2017; **13(1):**135-140.
17. Joshi KA, Shende P. *International Journal of Research in Pharmacology & Pharmacotherapeutics,* 2016; **5(3):**
18. Chandra Kant B, Joshi KA. *Heterocyclic Letters*, 2014; **4(1):**65-71.
19. Chauhan V, Joshi KA, Ram HK. *International Journal for Pharmaceutical Research Scholars*, 2015; **4(4):**178-182.
20. Kharatkar R, Joshi KA. *Journal of Pharmaceutical Science Bioscientific Research,* 2015; **5(5):**515-519.