REVIEW

CROATICA CHEMICA ACTA

Croat. Chem. Acta **2022**, *95*(2), 39–48
Published online: February 7, 2023
DOI: 10.5562/cca3899

HKD 1926

Antimicrobial Potential of Carbazole Derivatives

Vijay A. Kadnor

Department of Chemistry, Arts, Commerce & Science College (Affiliated to Savitribai Phule Pune University, Pune), Satral, Ahmednagar- 413711(MS), India
vijaykadnor11@gmail.com

RECEIVED: June 29, 2022 ✶ REVISED: November 8, 2022 ✶ ACCEPTED: November 10, 2022

Abstract: Amongst many nitrogen-containing heterocycles, carbazole frame is the building block of various biologically active compounds, including both synthetic and natural products of which its antimicrobial and antifungal activities are the most examined. In this review, 3, 4 and *N*- substituted carbazole derivatives and their antimicrobial activities are discussed (articles published from 2013 to 2022).

Keywords: carbazole derivatives, biological potential, antibacterial, antifungal.

INTRODUCTION

RESEARCH on novel chemotherapy has been very important in controlling different types of diseases in humans and animals caused by microorganisms. Various chemotherapeutic agents are isolated from living organisms known as antibiotics such as penicillin and tetracycline or they are certain synthetic organic compounds such as sulpha drug.[1] Microorganisms generated disease have the capacity to resist these chemotherapeutic agents, thus such microbial strains produce a major effort in the treatment of microbial infections.[2] To overcome this intricacy study of new antimicrobial agents is a continual process, which led to develop new chemical compounds with good antimicrobial activities and suitable to be used as chemotherapeutic agents.

The heterocyclic framework of aromatic carbazole is an advantageous pharmacophore skeleton found in various biologically active compounds from different sources, covering both natural and synthetic sources. The parent compound 9*H*-carbazole was first described by Graebe and Glaser in 1872, which was obtained from the anthracene fraction of coal tar distillate.[3] This outline has since grown the consideration by researchers as it has been highlighted in molecules that intervene a wide range of biological activities.[4,5] The biological properties of active carbazole alkaloids, isolated mainly from taxonomically similar plants of the genus *Murraya,*[6–9] *Clausena*[10–12] and *Glycosmis*[13–15] that belongs to the citrus family *Rutaceae* caused that many research groups became interested in the structural modifications of natural compounds and synthesis of new derivatives of carbazole.[16] The biologically active fused aromatic systems are known of natural origin (alkaloids) or synthetic drugs containing component of carbazole[17–26] in their structure which possess anti-cancer, antibacterial, antifungal, anti-inflammatory, hepatoprotective, anti-HIV, antiprotozoan and sedative properties, or topoisomerase II inhibition ability.

In this article I will present the antimicrobial potential of carbazole derivatives reported from the years 2013 to 2022, which are interesting because of their biological and photophysical properties.[27–46] Some of carbazole compounds have a very high activity against many organisms, bacteria, fungi, parasites.[34–38]

Antibacterial and Antifungal Activities of Carbazoles

A potent antibacterial activity of *N*-substituted benzimidazole incorporating with carbazole namely *N*-((1-(4-(9*H*-carbazol-9-yl) butyl)-1*H*-benzo[d]imidazol-2-yl) methyl)-2-fluoroaniline **1** and its corresponding salt **1a** (Figure 1.) reported by HuiZhen and coworkers in 2013.

The antibacterial activity revealed that carbazole **1** gave good antibacterial activity against *B. subtilis* (MIC = 64 μg/mL) and *P. aeruginosa* (MIC = 64 μg/mL), than the reference drug chloromycin. Corresponding salt compound **1a** showed the best antibacterial activity, at the concentrations of 8–32 μg/mL, it is more sensitive to the

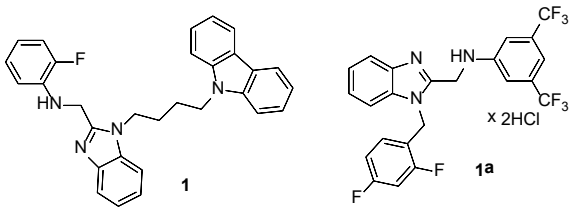


Figure 1. Structures of carbazole frame benzimidazole and its salt.[47]

S. aureus, *B. subtilis*, and *M. luteus* species (MIC = 8 μg/mL) which was nearly equipotent or even higher to the reference drug chloromycin 8 μg/mL. The study has shown the introduction of carbazole ring was advantageous to the benzimidazole for enhancement antimicrobial activity.[47]

Synthesis and spectral characterization of sulfonamide and carbamate derivatives of 4-(oxiran-2-ylmethoxy)-9*H*carbazole (**2a–d** and **3a–f**) as shown in Figure 2. were described by

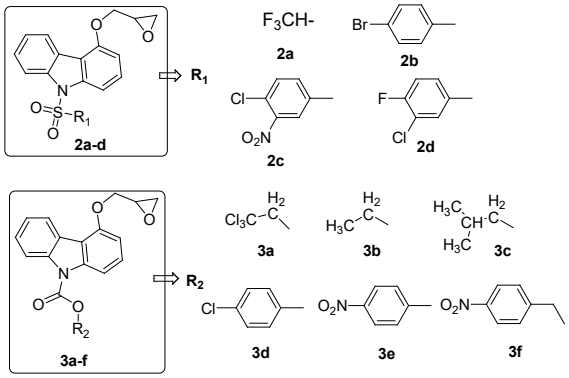
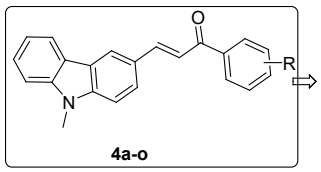
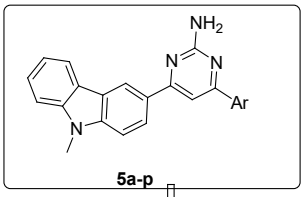


Figure 2. Structures of carbazole based sulfonamide and carbamate (**2a–d** and **3a–f**) derivatives.[48]

Venkata *et al*. in 2013, in order to study the change in substituent might affect the antimicrobial activity. Antimicrobial property of all the synthesized compounds (**2a–d** and **3a–f**)





Comp.	R	Comp.	R
4a	H	**4i**	2,4-Cl
4b	4-OCH_3	**4j**	3,4-Cl
4c	3,4-OCH_3	**4k**	2,5-Cl
4d	2,4,6- OCH_3	**4l**	4-Br
4e	4-F	**4m**	4-NO_2
4f	2,4-F	**4n**	2-Thiophene
4g	3,4-F	**4o**	2-pyridine
4h	4-Cl		

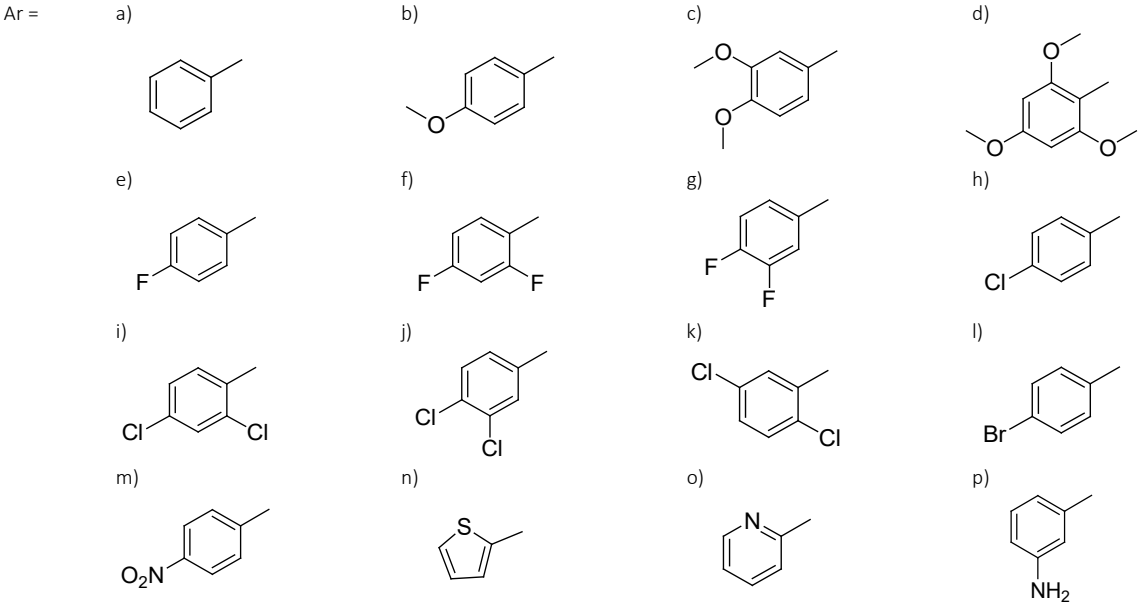
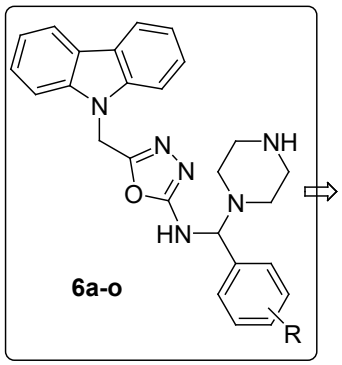


Figure 3. Structures of the carbazole derivatives reported by Bandgar et al.[49,50]



Comp.	R	Comp.	R
6a	4-NO_2	6i	2-OH
6b	4-OH	6j	3-Cl
6c	3,4, 5-OCH_3	6k	2-Cl
6d	4-Cl	6l	3 -OCH_3
6e	4- $N(CH_3)_2$	6m	4 -OCH_3
6f	2- NO_2	6n	4-F
6g	4-OH	6o	H
6h	3- NO_2		

Figure 4. Structures of carbazole incorporated oxadiazole derivatives (**6a**–**o**).[51]

examined against (*S. aureus*, *B. subtilis*, and *E. coli*) bacterial and (*F. oxysporum*, *C. albicans*, and *A. niger*) fungal strains through the agar well diffusion method. All the compounds (**2a**–**d** and **3a**–**f**) discovered modest to strong antimicrobial activities at a concentration of 200 µg/mL, and the results were comparable to the standard drugs ciprofloxacin and fluconazole. Amongst the synthesized compounds, the functional groups such as *p*-NO_2 in **2a** and **3e**, *p*-Cl-*m*-NO_2 in **2c** against *C. albicans*, *p*-Br in **2b** against *E. coli*, *p*-F-*m*-Cl in **2d**, CCl_3 in **3a** and isobutyl in **3c** against *B. subtilis* might be responsible for good activity.[48]

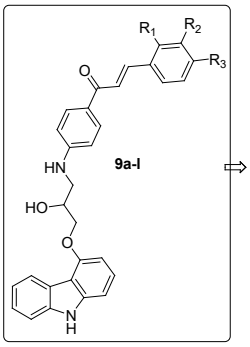
In 2013, Bandgar *et al*. evaluated the antimicrobial activities of a series of novel carbazole chalcones (**4a**–**o**) (Figure 3.). The antibacterial screening data of the compounds **4a**, **4e** and **4m** displayed significant inhibition zone (4.5 ± 2.5 mm) against all the three bacterial growth. Whereas compounds **4b**, **4g** and **4h** inhibited (6.0 ± 1.5 mm) zone against *P. vulgaris* and *E. coli* selectively, but compounds **4c** and **4o** had valuable results against *S. aureus* with inhibition zone (2.5 ± 2.0 and 4.5 ± 1.5 mm) respectively. Compounds **4h** and **4m** showed good antifungal activity with inhibition zone (5.5 ± 5.0 mm), while the rest of the compounds were inactive against *C. albicans*.[49]

The pyrimidine moiety is one of the most exposed structures found in the nucleic acid. The same year, Bandgar *et al*. also described the antimicrobial activity of a series of new carbazole substituted aminopyrimidines (**5a**–**p**) as drawn in Figure 3. using the disk diffusion method. Carbazole derivatives **5c**, **5g**, **5j** and **5o** showed upright activity in the range of inhibition zone (18.0 ± 8.00 mm) against all designated bacterial strains at a concentration of 1 mg/mL as compared to standard drug tetracycline. Notably carbazole derivative **5o** showed comparable activity with inhibition zone (18 ± 10 mm) as that of standard, against *B. subtilis*. *S. aureus* and *S. flexenari*. On the other hand, compounds **5b**, **5c**, **5m** and **5o** showed good activity with inhibition zone (15 ± 10 mm) against selected fungal strains at a concentration of 1 mg/mL as compared to standard drug nystatin. Compounds **5m** and **5o** showed comparable activity with inhibition zone (14 ± 10 and 15 ± 12mm) respectively as that of standard, against *C. albicans* and *A. niger*.[50]

In 2014, Sharma *et al*. evaluated the antimicrobial activity of a series of new carbazole derivatives (**6a**–**o**) (Figure 4.) with oxadiazole moiety is one of the most perceptible pharmacophore integrated at position 9 of carbazole nucleus. The antimicrobial activity was interpreted in terms of diameter (mm) of the zone of inhibition by disc diffusion method on nutrient agar medium against four bacterial and two fungal strains. Among the screened carbazoles, **6a, 6d,** and **6n** were found to be more potent with inhibition zone (16.2 ± 0.1, 24.2 ± 0.1 and 23.6 ± 0.1mm) against all tested bacterial and fungal strains at a concentration 50 µg/mL respectively.[51]

Synthesis of solvent–free carbazole chalcones (**7a**–**i**) and its benzofuran derivatives (**8a**–**i**) (Figure 6) described by Ashok *et al*. in 2014. The antimicrobial activity was examined against Gram positive *S. aureus* (ATCC 6538), *B. subtilis* (ATCC 6633) and Gram negative *E. coli* (ATCC 25922), *K. pneumoniae* (ATCC 13883) bacterial and three pathogenic fungi, *F. oxysporum*, *A. nigerzeae*, and *A. flavus* strains at 20 and 40 µg/mL concentrations. All the compounds (**7a**–**i** and **8a**–**i**) revealed moderate to strong antimicrobial activities at concentration of 20 µg/mL, and the results were comparable to the standard drugs ciprofloxacin and amphotericin-B.[52]

In 2014, Malani *et al*. explored the antimicrobial activities of carbazonyloxy *β*-hydroxy amine-based chalcones (**9a**–**l**) as shown in Figure 5. by the broth dilution method. New chalcones were examined with bacteria *E. coli* (MTCC 443), *P. aeruginosa* (MTCC 1688), *S. aureus* (MTCC 96), *S. pyogenus* (MTCC 442C), Fungi *C. albicans* (MTCC 227), *A. clavatus* (MTCC 1323) taking ampicilin, chloramphenicol, ciprofloxacin, gentamycin, norfloxacin and nystatin as standard drugs respectively. From this study, it was determined that compounds **9b** and **9j** proved at least as persuasive as the reference drug ampicillin in the

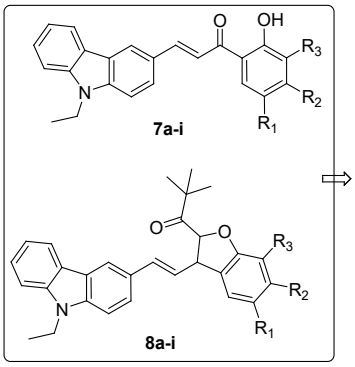


Comp.	R_1	R_2	R_3	Comp.	R_1	R_2	R_3
9a	H	H	OCH_3	**9g**	H	NO_2	OCH_3
9b	OH	H	H	**9h**	H	H	CH_3
9c	H	H	H	**9i**	H	H	H
9d	Cl	H	H	**9j**	H	H	OH
9e	H	H	Cl	**9k**	H	OCH_3	OCH_3
9f	H	NO_2	H	**9l**	H	H	NO_2

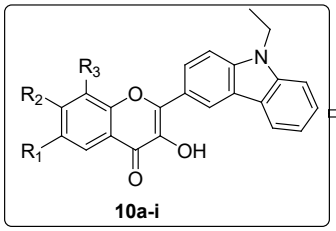
Figure 5. Structures of carbazonyloxy *β*-hydroxy amine-based chalcones (**9a–l**).[53]

case of *E. Coli*. The antifungal activity of compounds **9a**, **e**, **g** and **j** that they were comparable with the standard drug greseofulvin in the case of *C. albicans*, while compounds **4d** and **f** are more active compared with Greseofulvin in the case of *C. albicans*.[53]

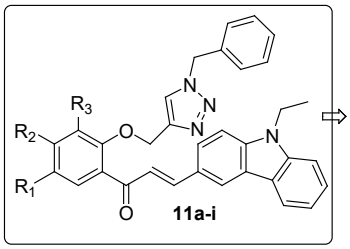
Antimicrobial activities of carbazole incorporated chromones (**10a–i**) as drawn in Figure 6. reported by Ashok and colleagues in 2015**.** The antimicrobial activity examined against four bacterial and two fungal strains using agar diffusion and poison plate technique express in terms



Comp.	R_1	R_2	R_3	Comp.	R_1	R_2	R_3
7a	H	H	H	**8a**	H	H	H
7b	F	H	H	**8b**	F	H	H
7c	Cl	H	H	**8c**	Cl	H	H
7d	Br	H	H	**8d**	Br	H	H
7e	CH_3	H	H	**8e**	CH_3	H	H
7f	Cl	CH_3	H	**8f**	Cl	CH_3	H
7g	Cl	H	H	**8g**	Cl	CH_3	H
7h	H	OCH_3	Cl	**8h**	H	OCH_3	H
7i	H	OC_2H_5	H	**8i**	H	OCH_3	H

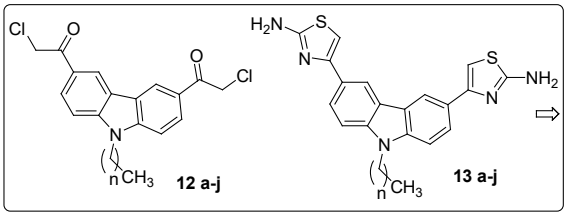


Comp.	R_1	R_2	R_3	Comp.	R_1	R_2	R_3
10a	H	H	H	**10f**	Cl	CH_3	H
10b	F	H	H	**10g**	Cl	H	Cl
10c	Cl	H	H	**10h**	H	OCH_3	H
10d	Br	H	H	**10i**	H	OC2H5	H
10e	CH_3	H	H				



Comp.	R_1	R_2	R_3	Comp.	R_1	R_2	R_3
11a	H	H	H	**11f**	Cl	CH_3	H
11b	F	H	H	**11g**	Cl	H	Cl
11c	Cl	H	H	**11h**	H	OCH_3	H
11d	Br	H	H	**11i**	H	OC2H5	H
11e	CH_3	H	H				

Figure 6. Structures of the carbazole derivatives reported by Ashok *et al* (2014, 2015, 2016).[52,54,55]



12, 13:

a, *n* = 1 b, *n* = 2 c, *n* = 3

d, *n* = 4 e, *n* = 5 f, *n* = 6

g, *n* = 7 h, *n* = 9 I, *n* = 15

J, *n* = 17

Figure 7. Structures of carbazole aminothiazoles (**13a–j**), their forerunner (**12a–j**).[56]

zone of inhibition diameter (mm). Amongst all, compounds **10a**, **10h** and **10i** showed maximal zones of inhibition in the range of (30–12 mm, 32–13 mm, 33–14 mm), respectively, against the tested bacterial and fungal strains. The study exposed the importance of 3-hydroxy chromenones with electron releasing groups, such as methoxy, ethoxy and unsubstituted compounds, showed the maximum activity.[54]

In 2016, Ashok et al. also reported the novel series of 1,2,3- triazolo- carbazole chalcones (**11a–i**) as depicted in Figure 6. and examined against a panel of bacterial and fungal microorganism by the agar diffusion and poison plate technique using ciprofloxacin, tetracycline and hymexazole standard drugs respectively. The zone of inhibition (in mm) was compared with standard drugs, antimicrobial data revealed that compounds **11e**, **11g**, and **11h** showed maximum zone of inhibition in the range of (23.5–15.8mm, 24.2–16.7mm and 24.5–14.2mm) respectively against Gram-positive and negative bacterial strains at the concentration of 20 µg/mL, as compared the standards tetracycline. Among all, compounds **11e**, **11f**, **11g**, **11h** and **11i** showed maximum activity against the tested fungal strains.[55]

In 2016, Addla *et al*. reported the preparation of new carbazole aminothiazoles and their precursor's (**13a–j** and **12a–j**) as DNA-targeting prospective antimicrobial agents (Figure 7.). All new compounds were examined against four Gram-positive bacteria, four Gram-negative bacteria and five fungi by the standard two folds serial dilution method using chloromycin, norfloxacin and fluconazole as standard drugs. The antimicrobial data revealed that, better antibacterial efficacies in preliminary active screening displayed by the carbazole aminothiazoles (**13a–j**) than their precursors (**12a–j**) which exposed that the 2-aminothiazole fragment was important in exerting antimicrobial activities. Noticeably heptyl derived carbazole aminothiazole **13f** could efficiently inhibit the growth of methicillin-resistant *S. aureus* (MRSA) with a MIC value of 4 µg/mL, which was greater to the reference drugs. Compounds **13h** and **13i** exhibited good activities against fluconazole-insensitive *A. flavus* with MIC value 128 µg/mL as compared to that fluconazole (MIC = 256 µg/mL). Study also exposed moderation in length of alkyl groups exhibited good activities against some tested bacteria. Specifically, *N*-pentyl carbazole aminothiazole **13d** displayed strong inhibition against *P. aeruginosa* with a MIC value of 2 µg/mL, which was 8-fold more active than reference drug chloromycin (MIC = 16 µg/mL). From this study, it was determined that prepared compounds with long hydrophobic alkyl chains such as pentyl and heptyl groups showed superior antimicrobial activities.[56]

In 2017, Clausen *et al*. reported four *N*-substituted carbazoles (**14a–d**) (Figure 8.) in order to study the inhibition activity of the fungal plasma membrane H^+-ATPase, which is necessary for fungal growth and survival**.** The H^+-ATPase inhibitory activity of the synthesized compounds conducted at a concentration of 20 µM. The compounds were characterized for H^+-ATPase inhibition and antifungal activity by means of an ATP hydrolysis assay and a fungal growth inhibition assay, respectively. The study has shown that compounds (**14a–d**) were identified as novel H^+-ATPase inhibitors and the ATP hydrolysis IC_{50} was determined together with antifungal activity against *S. cerevisiae* and *C. albicans.* Notably compound **14d** with two chloro substituents was recognized as the most potent antifungal compound, which displayed H^+-ATPase inhibitory activity. Also compound **14a** displayed the highest potency for H^+-ATPase inhibition, with IC_{50} values of 1.1 and 2 mM for *C. albicans* and *S. cerevisiae* H+-ATPase, respectively, as compared to the parent compounds.[57]

PLX01107 and **PLX01008** are xenomycins as drawn in Figure 9., new subclass of antimicrobial carbazole derivatives were designed and prepared by Zhanataev *et al.* in 2017. Both newly synthesized compounds showed strong antifungal activity *in vitro* and examine potential genotoxicity. The

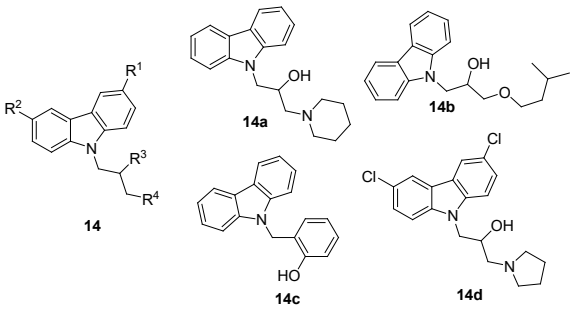


Figure 8. Carbazole scaffold (left) and structures of initial H^+-ATPase inhibitor hits.[57]

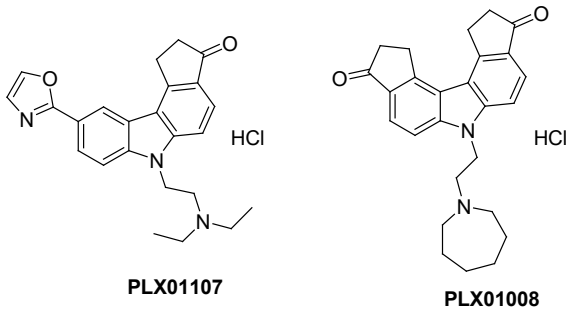


Figure 9. Structures of xenomycins **PLX01107** and **PLX01008**.[58]

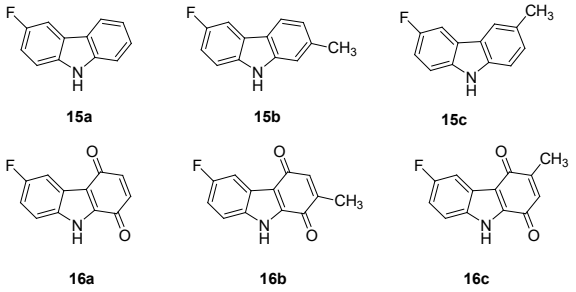


Figure 10. Structures of fluorocarabazole and its quionone derivatives (**15a–c** and **16a–c**).[59]

antimicrobial activity performed by bacterial reverse mutation assay (Ames test), *in vitro* cytokinesis-block micronucleus assay, and chromosome aberration test in mouse bone marrow cells, to investigate the possible genotoxicity of these compounds. The bacterial reverse mutation assay was performed with *S. typhimurium* TA98, TA100, TA1535, TA1537 and combination of *E. coli* WP2 uvrA and WP2 [pKM101] bacterial strains using the Ames MPF™ PENTA I kit and Aroclor 1254-induced rat liver fraction S9. The results obtained by Ames assays observed that, **PLX01107** did not show a progressive response for *S. typhimurium* or *E. coli* strains in the absence or presence of S9, but it displayed a cytotoxic response for strains TA98, TA100, and TA1535 without S9. In contrast, **PLX01008** was found to be mutagenic in *S. typhimurium* strains TA98 and TA1537, with or without S9 activation. The strain TA1535 indicated optimistic response only at 0.4 µg/mL in the absence of S9.[58]

In 2017, Chakraborty *et al*. reported the preparation and antimicrobial activities of fluorocarabazole and their respective quinone derivatives (**15a–c** and **16a–c**) as presented in Figure 10. using standard agar well diffusion method (NCCLS 2000).

Compound **15b** and its corresponding quinone compound **16b** showed the positive activity against *E. coli*, *B. subtilis* and Methicillin-resistant *S. aureus* with MIC value 25 µg/mL. Also compound **15c** and **16c** showed optimistic activity against *E. coli* and *S. aureus* with MIC value 50 µg/mL. The present study lead to the conclusion that properly substituted fluorocarbazole and fluorocarbazole quionones are highly promising scaffolds for further antimicrobial evaluation.[59]

Chromone is a natural molecule existing in the diet of human and animals and shows less toxicity to mammalian cells. In 2018, Kadnor *et al*. examined the antimicrobial activity of new carbazole substituted chromone derivatives (**17a–d, 18a–d** and **19a–d**) as drawn in Figure 11. using agar diffusion method ampicillin as standard drug. Carbazole derivatives **17b** and **17d** exhibited strong activities against Gram positive bacteria *S. lactis* and inhibit the growth of *Penicillium sp.* and *C. albicans* fungal strain as compare to the standard drug ampicillin. Notably, Compound **18a** gave nearly equipotent antibacterial broader bioactive spectrum against *P. putide B. subtilis* and *S. lactis* strains as compared to the standard drugs, while compounds **19b** and **19c** exhibited a broad spectrum against *S. lactis* bacterial strain. The results also suggested that electron withdrawing substituent chlorine and bromine on aromatic ring were more active against all test microbes than compounds with electron donating ones.[60] The same year, Kadnor and coworkers also investigated new 9-ethyl-9*H*-carbazole-3-carboxylic acid derivatives (**20a–e, 21a–e** and **22a–e**) as depicted in Figure 11. Carbazole acid derivatives were examined against four bacteria (*E. coli, P. putide, B. subtilis*, and *S. lactis*) and three fungi (*A. niger, Penicillium sp.* and *C. albicans*) by agar well diffusion method using ampicillin and greseofulvin as positive control. Compounds **20a**, **20b** and **20c** gave stronger antibacterial efficacies and broader bioactive spectrum

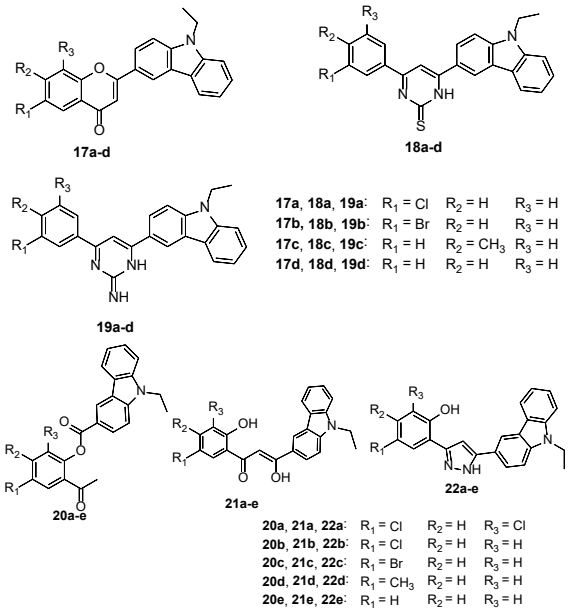


Figure 11. Structures of the carbazole derivatives reported by Kadnor *et al*.[60,61]

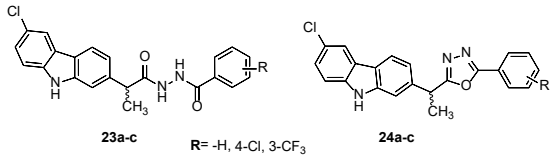
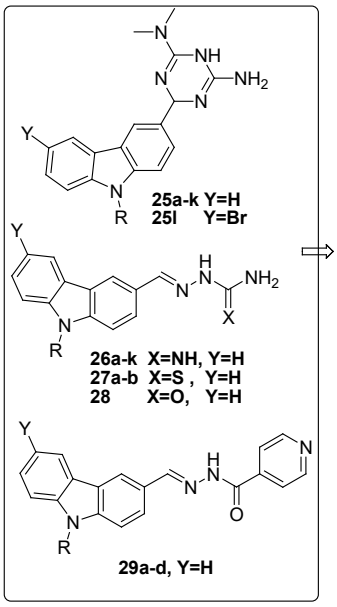


Figure 12. Structures of 6-chloro-9*H*-carbazol and 1,3,4-oxadiazol derivatives.[62]

against *S. lactis*, and *B. subtilis* with the MIC values in the range (30–40 μg/mL) and broad spectrum of antifungal activities (45–55 μg/mL) against *C. albicans* and *Penicillium sp.* as comparable to the standard drug ampicillin and griseofulvin (25 μg/mL) respectively. Compounds **21a**, **21b**, **21c, 21d** and **21e** displayed significant inhibition activities with a MIC ≥ 30 μg/mL against all tested fungal strains, while compounds **21d** and **21e** are passive for *C. albicans* fungal strain. Carbazole based pyrazoles **22a** and **22b** show remarkable antibacterial activity against tested pathogens, namely *S. lactis*, *B. subtilis* and *P. putide* compared to standard drug ampicillin at lowest concentration ranging from (35−55 μg/mL) with nearly equipotent of inhibition zone.[61]

In 2020, Bordei Telehoiu *et al*. reported the synthesis of 6-chloro-9*H*-carbazol and 1,3,4-oxadiazol scaffolds (**23a–c** and **24a–c**) as drawn in Figure 12. This novel adducts were examined against a panel of Gram-negative *E. coli* (ATCC 25922), *P. aeruginosa* (ATCC 27853) and Gram-positive *S. aureus* (ATCC 25923), *E. faecalis* (ATCC 29212) bacteria, as well as the fungal strain *C. albicans* (ATCC 90029) using the microdilution method in liquid Mueller Hinton medium at a concentrations in the range of 5–0.009 mg/mL. The best antibacterial was recorded for **23a** against *E. coli*, with MIC of 1.25 mg/mL and for **24c** against *C. albicans*, with MIC of 0.625 mg/mL.[62]

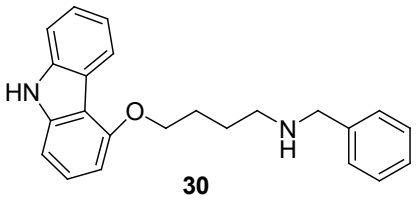
In 2021, Xue and coworkers synthesized a collection of 30 compounds with carbazole moiety containing an aminoguanidine, dihydrotriazine, thiosemicarbazide, semicarbazide or isonicotinic moiety (**25a–l**, **26a–k**, **27a–b**, **28**, and **29a–d**) as depicted in Figure 13. These thirty derivatives were screened against two Gram-positive strains *S. aureus* (4220), *S. mutans* (3289), one clinical isolate of multidrug-resistant Gram-positive bacterial strain *Methicillin-resistant S. aureus* (CCA*RM* 3167), one Gram-negative strain *E. coli* (1924) and one fungus *C. albicans* (7535). The MIC values were obtained using a 96-well microtiter plate and a serial dilution method, with positive controls gatifloxacin and moxifloxacin and DMSO as a negative control. All microorganisms showed susceptibility to most of the compounds with MICs in the range of 1–64 μg/ml. Compounds **25f**, **25l**, **26d** and **26e** exhibited strong antibacterial activity against Gram-positive strains and one Gram-negative strain with MIC values of 0.5 or 1 μg/ml. In addition, compound **25f** demonstrated a strong inhibitory activity (MIC of 0.5 μg/ml) against *E. coli* 1924, which was four-fold greater than the activities of moxifloxacin and gatifloxacin with (MIC of 2 μg/mL). The phenyl ring substituted compounds **25a–l** and **26a–k** exhibited significant effect on the potency of antimicrobial activities. The antibacterial activities were as follows order: phenyl group > 2,4-dichloro-substitutions > 4-CH_3> halogen substitutions>benzyl group > 4-CN > alkyl group. Moreover,



R=

25a	CH_3-	**26d**	4-$CH_3C_6H_4CH_2$-
25b	C_2H_5-	**26e**	2-$FC_6H_4CH_2$-
25c	$C_6H_5CH_2$-	**26f**	2,4-$Cl_2C_6H_3CH_2$-
25d	4-$CH_3C_6H_4CH_2$-	**26g**	2$ClC_6H_4CH_2$-
25e	2-$FC_6H_4CH_2$-	**26h**	3-$ClC_6H_4CH_2$-
25f	2,4-$Cl_2C_6H_3CH_2$-	**26i**	4-$ClC_6H_4CH_2$-
25g	2$ClC_6H_4CH_2$-	**26j**	4-$BrC_6H_4CH_2$-
25h	3-$ClC_6H_4CH_2$-	**26k**	4-$CNC_6H_4CH_2$-
25i	4-$ClC_6H_4CH_2$-	**27a**	CH_3-
25j	4-$BrC_6H_4CH_2$-	**27b**	C_2H_5-
25k	4-$CNC_6H_4CH_2$-	**28**	C_2H_5-
25l	C_6H_5-	**29a**	$C_6H_5CH_2$-
26a	CH_3-	**29b**	4-$CH_3C_6H_4CH_2$-
26b	C_2H_5-	**29c**	2-$FC_6H_4CH_2$-
26c	$C_6H_5CH_2$-	**29d**	2,4-$Cl_2C_6H_3CH_2$-

Figure 13. Structures of the carbazole derivatives reported by Xue and coworkers.[63]



30

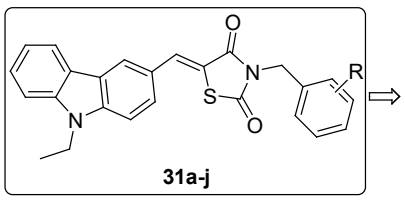
Figure 14. Structure of (4-(4-(benzylamino)butoxy)-9*H*-carbazole) derivative **30**.[64]

bromo- and chloro-substitutions on the phenyl ring in compounds **25a–l** were observed to improve their antifungal activity against *C. albicans* 7535.[63]

In 2021, Zawadzka and collegues reported (4-(4-(benzylamino)butoxy)-9*H*-carbazole) derivative **30** (Figure 14.) was prepared in two substitution steps from commercially available 4-hydroxycarbazole following standard procedures. This new adduct was studied against a Gram-positive *S. aureus* (ATCC 29213), *S. aureus* (ATCC 25923), *S. aureus* (ATCC 6358), *S. aureus* (ATCC 700699), *S. aureus* (ATCC 43300), *S. epidermidis* (ATCC 12228), *S. pyogenes* (ATCC 19615) and Gram-negative *E. coli* (ATCC 25922), *P. hauseri* (ATCC 13315), *P. aeruginosa* (ATCC 15442) bacteria, as well as fungi *C. albicans* (ATCC 10231), *A. flavus* (ATCC 9643).

Antimicrobial study exposed, that fungi and Gram-negative bacteria were more resistant than Gram-positive strains, although a positive control is needed to fully assess these bacterial strains.[64]

Lastly, Kamala and coworkers reported the series of novel carbazole thiazolidinedione hybrid derivatives (**31a–j)** as drawn in Figure 15. This adduct were examined against gram-positive bacterial strains (*S. aureus*) and gram-negative bacterial strains (*P. aeruginosa*, *E. coli*, *K. pneumonia*) at concentration of 100 µg/mL. The results were compared with the activity of the standard antibiotic ciproflaxacin and expressed as zone of inhibition in millimeter. Compounds **31c** and **31h** with nitro at second and bromo at fourth position on phenyl ring respectively have shown good antibacterial activity. On the other hand unsubstituted **31a**, chloro substituted **31d**, **31e**, **31f**, **31i**, fluoro substituted **31g** and cyano substituted **31j** compound have shown modest zone of inhibition.[65]



31a-j

31a	R = H	**31f**	R = 4-Cl
31b	R = 4-NO_2	**31g**	R = 4-F
31c	R = 2-NO_2	**31h**	R = 2-Br
31d	R = 2-Cl	**31i**	R = 2,4-Cl
31e	R = 3-Cl	**31j**	R = 4-CN

Figure 15. Structures of carbazole-thiazolidinedione hybrid derivatives (**31a–j**).[65]

CONCLUSIONS

This review summarizes acknowledged reports about various carbazole derivatives and their antimicrobial activities that are attractive structural patterns in synthetic organic chemistry due to their tunable electronic and steric properties. As summarized above, the existence of carbazole moieties has confirmed operative in improving the antimicrobial activity of various compounds. Several carbazole derivatives displayed strong *in vitro* inhibitory activity against bacteria and fungi with analogous or even greater activity when compared to the standard drugs. Consequently, this review may therefore propose an important resource to assist scientists in designing of new, convincing, and safe carbazole derivatives against microbial diseases in the near future**.**

REFERENCES

[1] P. Rajakumar, K. Sekar, V. Shanmugaiah, N. Mathivanan, *Bioorg. Med. Chem. Lett.* **2008**, *18*, 4416–4419. https://doi.org/10.1016/j.bmcl.2008.06.047.

[2] J. Salimon, N. Salih, E. Yousif, A. Hameed, A. Kreem, *Arabian J. Chem*. **2010**, *3*205–210. https://doi.org/10.1016/j.arabjc.2010.06.001.

[3] C. Graebe, C. Glaser, Ueber Carbazol, *Liebigs Ann. Chem*. **1872**, *163*, 343–360. https://doi.org/10.1002/jlac.18721630305.

[4] M. Kathiravan, A. Salake, A. Chothe, P. Dudhe, R. Watode, M. Mukta, S. Gadhwe, *Bioorg. Med. Chem*. **2012**, *20*, 5678–5698. https://doi.org/10.1016/j.bmc.2012.04.045

[5] T. Tasneem, R. K. Ravindra, T. M. Gireesh, K. H. Raveendra, B. M. Sheetal, *Eur. J. Med. Chem.* **2011**, *46*, 4366–4373. 10.1016/j.ejmech.2011.07.007

[6] Y. Tachibana, H. Kikuzaki, N. H. Lajis, N. Nakatani, *J. Agric. Food Chem.* **2001**, *49*, 5589–5594. https://doi.org/10.1021/jf010621r

[7] R. S. Ramsewak, M. G. Nair, G. M. Strasburg, D. L. DeWitt, J. L. Nitiss, *J. Agric. Food Chem.* **1999**, *47*, 444–447. https://doi.org/10.1021/jf9805808

[8] D. Chakraborty, B. Barman, P. Bose, *Tetrahedron* **1965**, *21*, 681–685. https://doi.org/10.1016/S0040-4020(01)82240-7

[9] J. Reisch, O. Goj, A. Wickramasinghe, H. BandaraHerath, G. Henkel, *Phytochemistry* **1992**, *31*, 2877–2879. https://doi.org/10.1016/0031-9422(92)83651-E

[10] T.-S. Wu, S.-C. Huang, P.-L. Wu, C.-M. Teng, *Phytochemistry* **1996**, *43*, 133–140. https://doi.org/10.1016/0031-9422(96)00212-9

[11] L. Wen-Shyong, J. D. McChesney, F. S. El-Feraly, *Phytochemistry* **1991**, *30*, 343–346. https://doi.org/10.1016/0031-9422(91)84151-H

[12] A. Chakraborty, B. Chowdhury, P. Bhattacharyya, *Phytochemistry* **1995**, *40*, 295–298. https://doi.org/10.1016/0031-9422(95)00047-B

[13] A. K. Chakravarty, T. Sarkar, K. Masuda, K. Shiojima, *Phytochemistry* **1999**, *50,* 1263–1266. https://doi.org/10.1016/S0031-9422(98)00666-9

[14] C. Ito, M. Itoigawa, A. Sato, C. M. Hasan, M. A. Rashid, H. Tokuda, T. Mukainaka, H. Nishino, H. Furukawa, *J. Nat. Prod*. **2004**, *67*, 1488–1491. https://doi.org/10.1021/np0400611

[15] A. Chakraborty, B. Chowdhury, S. Jash, G. Biswas, S. Bhattacharyya, P. Bhattacharyya, *Phytochemistry* **1992**, *31*, 2503–2505. https://doi.org/10.1016/0031-9422(92)83310-U

[16] H. J. Knolker, K. R. Reddy, *Chem. Rev*. **2002,** *102*, 4303–4427. https://doi.org/10.1021/cr020059j

[17] P. B. Arimondo, P. Moreau, A. Boutorine, C. Bailly, M. Prudhomme, J.-S. Sun, T. Garestier, C. Helene, *Bioorg. Med. Chem*. **2000**, *8*, 777–784. https://doi.org/10.1016/S0968-0896(00)00012-2

[18] C. Bailly, *Curr. Med. Chem*. **2000**, *7*, 39–58. https://doi.org/10.2174/0929867003375489

[19] J. Benoit, M. Facompre, H. Da Costa, S. Routier, J.-Y. Merour, P. Colson, C. Houssier, C. Bailly, *Bioorg. Med. Chem*. **2001**, *9*, 1533–1541. https://doi.org/10.1016/S0968-0896(01)00026-8

[20] C. Asche, W. Frank, A. Albert, U. Kucklaender, *Bioorg. Med. Chem*. **2005**, *13*, 819–837. https://doi.org/10.1016/j.bmc.2004.10.038

[21] N. Haider, *Curr. Org. Chem*. **2006**, *10*, 363–375. https://doi.org/10.2174/138527206775473913

[22] T. Lemster, U. Pindur, G. Lenglet, S. Depauw, C. Dassi, M.-H. David-Cordonnier, *Eur. J. Med. Chem*. **2009**, *44*, 3235–3252. https://doi.org/10.1016/j.ejmech.2009.03.026

[23] M. G. Ferlin, C. Marzano, V. Gandin, S. DallAcqua, L.D. Via, *Chem. Med. Chem*. **2009**, *4,* 363–377. https://doi.org/10.1002/cmdc.200800368

[24] C. Ito, M. Itoigawa, K. Aizawa, K. Yoshida, N. Ruangrungsi, H. Furukawa, *J. Nat. Prod*. **2009**, *72*, 1202–1204. https://doi.org/10.1021/np800735m

[25] U. Songsiang, T. Thongthoom, C. Boonyarat, C. Yenjai, A. D. Claurailas, *J. Nat. Prod*. **2011**, *74*, 208–212. https://doi.org/10.1021/np100654m

[26] J. Wang, Y. Zheng, T. Efferth, R. Wang, Y. Shen, X. Hao, *Phytochemistry*, **2005**, *66*, 697–701. https://doi.org/10.1016/j.phytochem.2005.02.003

[27] F.-F. Zhang, L.-L. Gan, C.-H. Zhou, *Bioorg. Med. Chem. Lett*. **2010**, *20*, 1881–1884. https://doi.org/10.1016/j.bmcl.2010.01.159

[28] M. Saravanabhavan, K. Sathya, V. G. Puranik, M. Sekar, *Spectrochim. Acta A Mol. Biomol. Spectrosc*. **2014**, *118*, 399–406. https://doi.org/10.1016/j.saa.2013.08.115

[29] H.-Y. Lee, Y. Jung, W. Kim, J. H. Kim, M.-S. Suh, S. K. Shin, H.-J. Yoon, *Bioorg. Med. Chem. Lett*. **2008**, *18*, 4670–4674. https://doi.org/10.1016/j.bmcl.2008.07.006

[30] J. Molette, J. Routier, N. Abla, D. Besson, A. Bombrun, R. Brun, H. Burt, K. Georgi, M. Kaiser, S. Nwaka, M. Muzerelle, A. Scheer, *ACS Med. Chem. Lett*. **2013**, *4*, 1037–1041. https://doi.org/10.1021/ml400015f

[31] B. P. Bandgar, L. K. Adsul, H. V. Chavan, S. S. Jalde, S. N. Shringare, R. Shaikh, R. J. Meshram, R. N. Gacche, V. Masand, *Bioorg. Med. Chem. Lett*. **2012**, *22*, 5839–5844. https://doi.org/10.1016/j.bmcl.2012.07.080

[32] A. Zall, D. Kieser, N. Heottecke, E. C. Naumann, B. Thomaszewski, K. Schneider, D. T. Steinbacher, R. Schubenel, S. Masur, K. Baumann, B. Schmidt, *Bioorg. Med. Chem*. **2011**, *19*, 4903–4909. https://doi.org/10.1016/j.bmc.2011.06.062

[33] W. Yang, Y. Wong, O.T.W. Ng, L.-P. Bai, D.W.J. Kwong, Y. Ke, Z.-H. Jiang, H.- W. Li, K. K. L. Yung, M. S. Wong, *Angew. Chem. Int. Ed*. **2012**, *51*, 1804–1810. https://doi.org/10.1002/anie.201104150

[34] S. Thiratmatrakul, C. Yenjai, P. Waiwut, O. Vajragupta, P. Reubroycharoen, M. Tohda, C. Boonyarat, *Eur. J. Med. Chem*. **2014**, *75*, 21–30. https://doi.org/10.1016/j.ejmech.2014.01.020

[35] I. Tasset, C. Espinola, F. J. Medina, M. Feijoo, C. Ruiz, E. Moreno, M. M. Gomez, J. A. Collado, C. Munoz, J. Muntane, P. Montilla, I. Tunez, *J. Physiol. Biochem*. **2009**, *65*, 291–296. https://doi.org/10.1007/BF03180581

[36] Y. Ouyang, Z. Chen, M. Tan, A. Liu, M. Chen, J. Liu, R. Pi, J. Fang, *Biochem. Biophys. Res. Commun*. **2013**, *441*, 917–922. https://doi.org/10.1016/j.bbrc.2013.10.160

[37] D. Zhu, M. Chen, M. Li, B. Luo, Y. Zhao, P. Huang, F. Xue, S. Rapposelli, R. Pi, S. Wen, *Eur. J. Med. Chem*. **2013**, *68*, 81–88. https://doi.org/10.1016/j.ejmech.2013.07.029

[38] L. Nagarapu, H. K. Gaikwad, K. Sarikonda, J. Mateti, R. Bantu, P. S. Raghu, K. M. Manda, S. V. Kalvendi, *Eur. J. Med. Chem*. **2010**, *45*, 4720–4725. https://doi.org/10.1016/j.ejmech.2010.07.004

[39] S. Yoon, J.-H. Kim, Y. J. Lee, M. Y. Ahn, G. Choi, W. K. Kim, Z. Yang, H. J. Lee, H. R. Moon, H. S. Kim, *Eur. J. Pharmacol*. **2012**, *697*, 24–31. https://doi.org/10.1016/j.ejphar.2012.10.001

[40] C. Saturnino, F. Grande, S. Aquaro, A Caruso, D. Iacopetta, M. G. Bonomo, P. Longo, D. Schols, M. S. Sinicropi, *Molecules* **2018**, *23*, 286. https://doi.org/10.3390/molecules23020286

[41] C. Asche, M. Demeunynck, *Med. Chem*. **2007**, *7*, 247–267. https://doi.org/10.2174/187152007780058678

[42] J. M. Wang, F. C. Huang, M. Hsin-JuiKuo, Z. F. Wang, T. Y. Tseng, L. C. Chang, S. J. Yen, T. C. Chang, J. J. Lin, *J. Biol. Chem*. **2014**, *289*, 14612–14623. https://doi.org/10.1074/jbc.M114.548230

[43] J. Li, D. Li, Y. Han, S. Shuang, C. Dong, *Spectrochim. Acta Part A* **2009**, *73*, 221–225. https://doi.org/10.1016/j.saa.2009.01.019

[44] A. Głuszynska, K. Bajor, I. Czerwinska, D. Kalet, B. Juskowiak, *Tetrahedron Lett*. **2010**, *51*, 5415–5418. https://doi.org/10.1016/j.tetlet.2010.07.180

[45] C. Bailly, *Curr. Med. Chem*. 2000, *7*, 39–58. https://doi.org/10.2174/0929867003375489

[46] P. Rajakumar, K. Sekar, V. Shanmugaiah, N. Mathivanan, *Eur. J. Med. Chem*. **2009**, *44*, 3040–3045. https://doi.org/10.1016/j.ejmech.2008.07.031

[47] Z. HuiZhen, L. JianMei, R. Syed, Z. ChengHe, *Sci. China Chem.* **2014**, *57*, 807–822. https://doi.org/10.1007/s11426-014-5087-x

[48] S. Venkata L. Reddy, K. Naresh, C. N. Raju, *Der Pharmacia Lettre* **2013**, 5, 221–231.

[49] B. P. Bandgar, L. K. Adsul, S. V. Lonikar, H. V. Chavan, S. N. Shringare, S. A. Patil, S. S. Jalde, B. A. Koti, N. A. Dhole, R. N. Gacche, A. Shirfule, *J. Enzyme Inhib. Med*. **2013**, *28*, 593–600. https://doi.org/10.3109/14756366.2012.663365

[50] L. K. Adsul, B. P. Bandgar, H. V. Chavan, S. S. Jalde, V. D. Dhakane, A. L. Shirfule, *J. Enzyme Inhib. Med*. **2013**, *28*, 1316–1323. 10.3109/14756366.2012.740477

[51] D. Sharma, N. Kumar. D. Pathak, *J. Serb. Chem. Soc.* **2014**, *79*, 125–132. https://doi.org/10.2298/JSC130123069S

[52] D. Ashok, R. Sidda, B. Vijaya Lakshmi, A. Ganesh, *Russ. J. Gen. Chem*. **2014**, *84*, 2211–2217. https://doi.org/10.1134/S1070363214110280

[53] M. H. Malani, B. Z. Dholakiya, *Res. Chem. Intermed*. **2014**, *40*, 127–137. https://doi.org/10.1007/s11164-012-0915-0

[54] D. Ashok, S. Ravi, B. Vijayalakshmi, A. Ganesh, *J. Serb. Chem. Soc*. **2015**, *80* (*11*), 1361–1366. https://doi.org/10.2298/JSC141203051A

[55] D. Ashok, S. Ravi, B. Vijayalakshmi, A. Ganesh, S. Adam, *Russ. J. Bioorg. Chem*. **2016**, *42*, 323–331. https://doi.org/10.1134/S1068162016030043

[56] D. Addla, S. Q. Wen, W. W. Gao, S. K. Maddili, L. Zhang, C. H. Zhou, *Med. Chem. Comm*. **2016**, *7*, 1988–1994. https://doi.org/10.1039/C6MD00357E

[57] J. D. Clausen, L. Kjellerup, K. O. Cohrt, J. B. Hansen, W. Dalby-Brown, A-M. L. Winther, *Bioorg. Med. Chem. Lett*. **2017**, *27*, 4564–4570. https://doi.org/10.1016/j.bmcl.2017.08.067

[58] A. K. Zhanataev, N. V. Eremina, Z. V. Chayka, V. I. Kazey, E. L. Andrianova, A. A. Purmal, E. B. Rydkina, A. D. Durnev, *Mutat. Res. Genet. Toxicol. Environ. Mutagen.* **2017**, *816*, 24–31. https://doi.org/10.1016/j.mrgentox.2017.03.004

[59] S. Chakraborty, B. Chakraborty A. Saha, C. Saha, T. K. Ghosh, I. Bhattacharyya, *Indian J. Chem.* **2017**, *56B*, 701–708.

[60] V. A. Kadnor, G. D. Shirole, S. N. Shelke, *Iran. JOC*. **2018**, *10*, 2343–2351.

[61] V. A. Kadnor, G. R. Mhaske, S. N. Shelke, *Croat. Chem. Acta*. **2018**, *91*, 367–375. https://doi.org/10.5562/cca3353

[62] A. T. Bordei Telehoiu, D. C. Nut, M. T. Caproiu, F. Dumitrascu, I. Zarafu, P. Ionit, C. D. Badiceanu, S. A. Avram, M. C. Chifiriuc, C. Bleotu, C. Limban, *Molecules* **2020,** *25*, 2–18. https://doi.org/10.3390/molecules25020266

[63] Y. J. Xue, M. Y. Li, X. J. Jin, C. J. Zheng, H. R. Piao, *J. Enzyme Inhib. Med*. **2021**, *36*, 296–307. https://doi.org/10.1080/14756366.2020.1850713

[64] K. Zawadzka, A. Felczak, I. E. Głowacka, D. G. Piotrowska, K. Lisowska, *Int. J. Mol. Sci*. **2021**, *22*, 1–12. https://doi.org/10.3390/ijms222312796

[65] L. Kamala, B. Sathish Kumar, P. V. Anantha Lakshmi, *Russ. J. Bioorg. Chem*. **2021**, Vol. 47, No. 1, pp. 166–173. https://doi.org/10.1134/S106816202101009X