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Synthesis and antimicrobial activities of novel 8-(1-alkyl/ /alkylsulphonyl/alkoxycarbonyl-benzimidazol-2- -ylmethoxy)-5-chloroquinolines

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Abstract: The synthesis of a series of novel 8-(1-alkyl/alkylsulphonyl/alkoxycarbonyl-benzimidazol-2-ylmethoxy)-5-chloroquinoline derivatives is reported. These derivatives were prepared by the condensation of *o*-phenylenediamine with [(5-chloroquinolin-8-yl)oxy]acetic acid, followed by substitution at nitrogen with different electrophilic reagents in presence of an appropriate base to give a series of nitrogen heterocycles containing the benzimidazole and quinoline nuclei. The structures of the compounds were confirmed based on ^{1}H-NMR, ^{13}C--NMR, IR and mass spectral data. Almost all the compounds exhibited promising antibacterial activity against *Salmonella typhimurium* and *Staphylococcus aureus.* Some of the compounds showed good antifungal activities against *Aspergillus niger* but the antifungal activities against *Candida albicans* were disappointing.

Keywords: heterocyclic; benzimidazole; quinoline; antibacterial; antifungal.

INTRODUCTION

Heterocyclic compounds containing the benzimidazole nucleus are well recognized for their different therapeutic activities.[1–6] Some of the important examples are lansoprazole (anti-ulcer),[7] carbendazim (fungicide),[8] thiabendazole (anthelmintic and fungicide),[9] benperidol (antipsychotic), oxatomide (anti-allergic and anti-asthmatic),[10] *etc*. Similarly, compounds containing the quinoline nucleus are also known for different therapeutic activities,[11,12] such as chloroquine (antimalarial),[13] chlorquinaldol (antibacterial and antifungal),[14] *etc*. (Fig. 1).

Thus, substituted benzimidazoles and quinolines both have potential biological activities. Hence, molecules containing both benzimidazole and quinoline as building blocks of their chemical structure have increased probability of possessing still better biological activities. In an attempt to extend the study of this

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class of heterocyclic compounds, a series of novel benzimidazole–quinoline compounds was synthesized. All the compounds were characterized with modern spectroscopic techniques. These compounds were subjected to biological screening, *i.e.*, antibacterial and antifungal activity against standard bacterial and fungal strains were determined. Their activities were compared with those of known standard drugs.

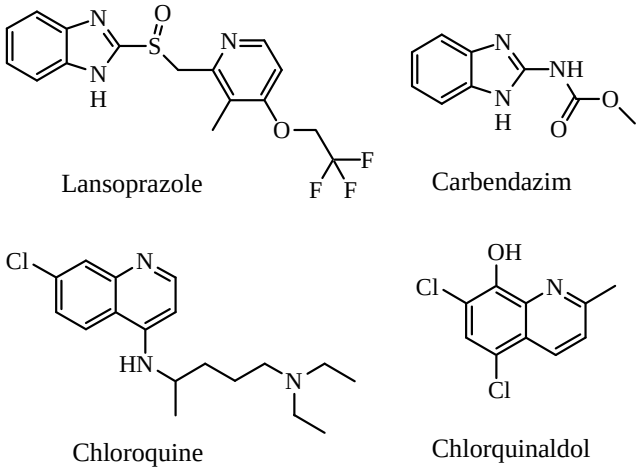


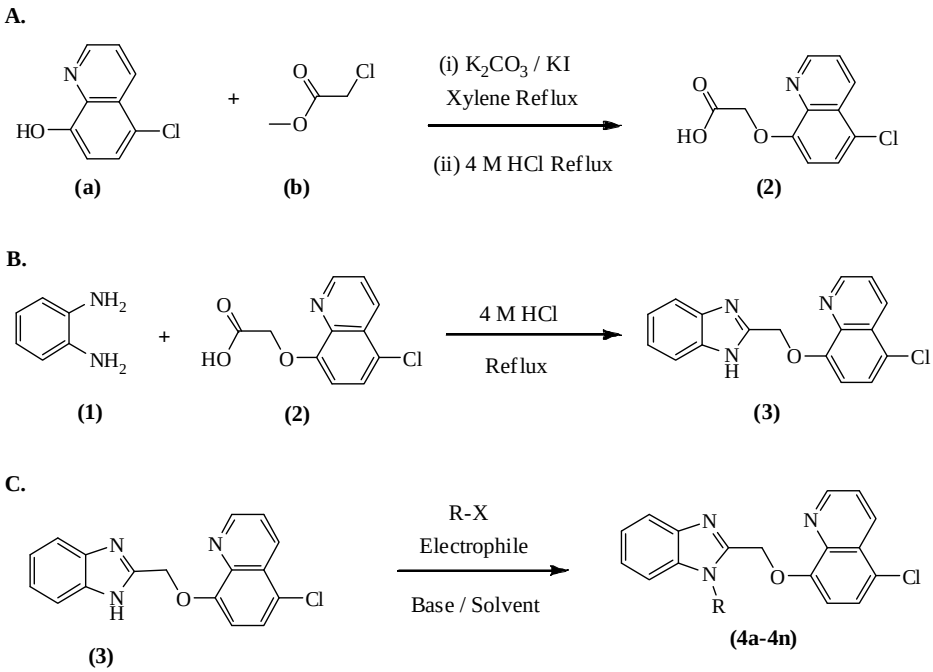
Fig. 1. Clinically used known drugs having either a benzimidazole or a quinoline nucleus.

RESULTS AND DISCUSSION

A series of novel heterocyclic compounds containing benzimidazole and quinoline nuclei was synthesized. Some other compounds of a similar type were reported by Goldfarb,[15] Bhat[16] and Dynachim (formerly known as Chimetron S. A. R. L.).[17,18] The intermediate [(5-chloroquinolin-8-yl)oxy]acetic acid (**2**) was prepared by a process similar to the known literature procedures,[19–21] using 5-chloro-8-hydroxyquinoline (**a**) and monochloroacetic acid methyl ester (**b**).

Ortho-phenylenediamine (OPDA) (**1**) was condensed with [(5-chloroquinolin-8-yl)oxy] acetic acid (**2**) in 4 M HCl under reflux[22] (Phillips conditions), as represented in Scheme 1. The reaction mixture was basified with aqueous sodium hydroxide, filtered and the crude product was crystallized from ethanol. Based on spectral and analytical data, the compound was assigned the structure 8-[(1*H*--benzimidazol-2-yl)methoxy]-5-chloroquinoline (**3**). Reaction of **3** with different electrophiles[23–26] in the presence of an appropriate base yielded a series of novel benzimidazoles **4a**–**n**, as represented in Scheme 1.

Synthesis of compounds **4a**–**g** was realized in DMF (*N*,*N*-dimethylformamide) using potassium *tert*-butoxide as the base. Complete conversion was achieved within 20 to 60 min at 60 °C. The products were isolated by quenching the reaction mass with cold water and filtering off the precipitated solid.



Where, X = Halogen;
(4a, R = Methyl), (4b, R = Ethyl), (4c, R = Propyl), (4d, R = Butyl), (4e, R = Pentyl), (4f, R =Benzyl), (4g, R =p-Bromobenzyl), (4h, R =methylsulfonyl), (4i, R =Phenylsulfonyl), (4j, R = p-Toluenesulfonyl), (4k = R = Methoxycarbonyl), (4l, R = Ethoxycarbonyl), (4m, R = Benzyloxycarbonyl), (4n, R = 2,2,2-Trichloroethoxycarbonyl).

Scheme 1. Synthetic route to compounds **4a**–**n**.

Preparation of derivatives **4h**–**n** from **3** was performed in pyridine as both the base and solvent using the corresponding alkyl/aryl sulphonyl chlorides or alkyl/aralkyl chloroformates. Reactions were fast and complete conversion could be achieved in 30 to 40 min at room temperature. Reaction mass was then quenched with water, neutralized with dilute hydrochloric acid and the product was extracted with ethyl acetate. Partial concentration of the organic layer and addition of diethyl ether into the concentrated mass resulted in precipitation of the required product, which was collected by filtration. The crude products were purified with a hot acetone–water mixture.

The compounds were characterized by ^{1}H-NMR, mass, FTIR and ^{13}C-NMR of some representative derivatives. Yields and reaction conditions are given in Table I. The melting points and spectral data are in the supplementary material to this paper.

Antimicrobial activity

All the synthesized compounds were subjected to *in vitro* antibacterial and antifungal activity determination.

Most of the compounds showed very good antibacterial activities against *Staphylococcus aureus* (Gram-positive) and *Salmonella typhimurium*, and were almost competitive with the standard drugs, chloramphenicol and ciprofloxacin. The results of the determination of the antibacterial activities are summarized in Table II.

TABLE I. Yields and reaction conditions of the synthesized compounds

Electrophile	Conditions	Substituent 'R'	Compd.	Yield, %
Methyl iodide	*t*-BuOK/DMF/60 °C	Methyl	**4a**	83
Ethyl iodide	*t*-BuOK/DMF/60 °C	Ethyl	**4b**	78
n-Propyl bromide	*t*-BuOK/DMF/60 °C	*n*-Propyl	**4c**	73
n-Butyl bromide	*t*-BuOK/DMF/60 °C	*n*-Butyl	**4d**	68
n-Pentyl bromide	*t*-BuOK/DMF/60 °C	*n*-Pentyl	**4e**	61
Benzyl bromide	*t*-BuOK/DMF/60 °C	Benzyl	**4f**	85
4-Bromobenzyl bromide	*t*-BuOK/DMF/60 °C	4-Bromobenzyl	**4g**	81
Methanesulphonyl chloride	Pyridine/RT	Methylsulphonyl	**4h**	62
Benzenesulphonyl chloride	Pyridine/RT	Phenylsulphonyl	**4i**	60
p-Toluenesulphonyl chloride	Pyridine/RT	4-Methylphenyl-sulphonyl	**4j**	52
Methyl chloroformate	Pyridine/RT	Methoxycarbonyl	**4k**	50
Ethyl chloroformate	Pyridine/RT	Ethoxycarbonyl	**4l**	68
Benzyl chloroformate	Pyridine/RT	Benzyloxycarbonyl	**4m**	55
2,2,2-Trichloroethyl chloroformate	Pyridine/RT	2,2,2-Trichloroethoxy-carbonyl	**4n**	67

TABLE II. Antibacterial activities of the novel benzimidazole derivatives and standard antibacterial drugs (zone of inhibition in mm)

Compound	*S. aureus* MTCC-96				*S. typhimurium* MTCC-98			
	Concentration, μg mL^{-1}							
	25	50	100	250	25	50	100	250
3	11	15	18	20	12	16	18	21
4a	10	14	17	18	13	14	15	16
4b	11	12	13	15	11	14	17	19
4c	14	16	17	19	15	17	18	18
4d	11	13	18	20	12	15	19	23
4e	10	12	16	17	15	15	18	19
4f	10	12	15	19	14	16	18	21
4g	10	11	13	14	15	16	18	20
4h	12	14	17	19	12	15	19	21
4i	13	15	16	18	12	12	15	18
4j	10	11	14	15	15	17	20	21
4k	13	15	18	19	12	13	17	19
4l	11	12	13	15	14	16	17	21
4m	11	14	16	17	12	13	15	17
4n	15	17	19	22	15	17	18	20
Chloramphenicol	14	19	20	21	12	18	19	21
Ciprofloxacin	19	21	22	22	18	19	20	21

Some of the compounds (**4a, 4i, 4j** and **4l**) exhibited good antifungal activities against *Aspergillus niger* but the antifungal activities against *Candida albicans* were poor as compared to the standard drug, griseofulvin. The results of the determination of the antifungal activities are summarized in Table III.

TABLE III. Antifungal activities of the novel benzimidazole derivatives and standard antifungal drug (zone of inhibition in mm)

Compound	*A niger* MTCC 282				*C. albicans* MTCC 227			
	Concentration, μg mL^{-1}							
	50	100	250	500	50	100	250	500
3	18	18	19	21	11	13	15	17
4a	19	22	22	24	12	13	15	16
4b	17	18	20	21	13	14	16	17
4c	17	21	22	23	11	13	16	17
4d	15	17	18	19	10	13	14	17
4e	17	18	19	20	11	12	15	16
4f	18	20	22	23	12	13	14	16
4g	17	18	20	21	12	14	16	17
4h	17	20	21	22	11	13	15	16
4i	18	21	23	25	12	14	15	17
4j	19	23	23	24	11	12	14	15
4k	18	20	20	21	12	15	17	18
4l	19	19	21	24	11	13	15	16
4m	17	18	22	23	11	15	16	17
4n	18	20	22	23	11	12	14	17
Griseofulvin	23	25	25	28	21	22	22	24

EXPERIMENTAL

TLC analysis was performed using pre-coated silica gel plates and visualization under a UV lamp. The melting points are uncorrected and were determined using a Polmon Melting Point Apparatus model No. MP96. The NMR spectra were recorded on a Bruker Avance II 400 MHz NMR spectrometer. The mass spectra were obtained using a Waters Q-ToF Micro spectrometer with an ESI source in the positive ion mode. The IR spectra were recorded on a Perkin-Elmer Spectrum One FTIR spectrometer. Analytical and spectral data of synthesized compounds are given in Supplementary material.

o-Phenylenediamine, 5-chloro-8-hydroxyquinoline, monochloroacetic acid methyl ester and the electrophilic reagents were obtained from commercial suppliers. All the employed solvents were of analytical grade.

*Synthesis of [(5-chloroquinolin-8-yl)oxy]acetic acid (**2**)*

A mixture of 5-chloro-8-hydroxyquinoline (**a**) (10 g, 0.056 mol), potassium carbonate powder (9.7 g, 0.07 mol) and potassium iodide (0.7 g, 0.0042 mol) in xylene (110 mL) was heated at reflux (140–144 °C) for 1 h with the simultaneous azeotropic removal of water. Reaction mass was then cooled to 90 °C and monochloroacetic acid methyl ester (**b**) (7.86 g, 0.072 mol) was slowly added over 1 h at 90–95 °C. The reaction mass was then further heated and refluxed for 5 h to obtain a clear brown-coloured solution, monitored by TLC. Xylene was distilled off at 55–60°C under vacuum, the residue cooled to RT and water added (100

mL). The resultant slurry was stirred at RT for 30 min, filtered and the solid washed with water. The wet cake was taken in 30 mL water, pH adjusted to 3 to 3.5 with conc. HCl (around 5 mL) and stirred at 50 °C for 1 h. The reaction mass was cooled to RT, filtered and the solid washed with water to afford 10.6 g of the title compound on drying.

*Synthesis of 8-[(1*H*-benzimidazol-2-yl)methoxy]-5-chloroquinoline (**3**)*

A mixture of OPDA (**1**) (15 g, 139 mmol) and [(5-chloroquinolin-8-yl)oxy]acetic acid (**2**) (33 g, 139 mmol) in 4 M hydrochloric acid (300 mL) was refluxed (98–100 °C) for 4 h. The reaction was monitored by TLC. The reaction mass was then cooled to room temperature, diluted with water (500 mL) and basified to pH 9 with 10 % aqueous sodium hydroxide solution at room temperature. The reaction mass was filtered and the obtained solid was washed with water. Crystallization of the crude product from ethanol afforded 35g of the title compound (**3**) on drying.

*General procedure for the synthesis of compounds **4a**–**g***

To a solution of compound **3** (1.5 g, 4.85 mmol) in DMF (45 mL) was added potassium *tert*-butoxide (0.559 g, 5.82 mmol) in small portions at 0–5 °C. After completion of the addition, the temperature of the reaction mass was raised to 5–10°C and stirred at this temperature for 15–20 min. The corresponding alkyl halide (5.82 mmol) was added into the reaction mass in 5–10 min at 5–10 °C and stirred for 15 min. The reaction mass was then heated to 60 °C and stirred at this temperature for 20–60 min; monitored by TLC. After complete conversion, the reaction mass was cooled to room temperature and quenched with cold water (200 mL). The obtained solid was filtered, washed with water and dried to yield the corresponding N-alkyl derivatives **4a**–**g**.

The corresponding alkyl halides used for the reactions were methyl iodide, ethyl iodide, *n*-propyl bromide, *n*-butyl bromide, *n*-pentyl bromide, benzyl bromide and 4-bromobenzyl bromide.

*General procedure for the synthesis of compounds **4h**–**n***

To a solution of compound **3** (1.5g, 4.85 mmol) in pyridine (15 mL) was added slowly over 10–15 min the respective alkyl/aryl sulphonyl chloride or alkyl/aralkyl chloroformate (5.82 mmol) at 0–5 °C. After completion of the addition, the temperature of the reaction mixture was allowed to rise slowly to room temperature and stirred at this temperature for 30–40 min. The reaction was monitored by TLC. After complete conversion, the reaction mass was quenched with water (45 mL) and 2 M HCl was added until the pH of the reaction mass was neutral. The product was extracted twice with ethyl acetate, the combined ethyl acetate layer was washed with water and dried with anhydrous sodium sulphate. The organic phase was then concentrated partially under vacuum to reduce the volume to 15 mL. Then 20 mL *tert*--butylmethyl ether was added at room temperature and stirred for 15 min. The precipitated solid was filtered and dried to obtain the corresponding N-alkylsulphonyl/alkoxycarbonyl derivatives **4h**–**n**. The crude compounds were crystallized from a hot acetone–water mixture.

Microbiological procedures for the activity study

For assessing their antibacterial activity, the compounds were cultured for 48 h against two pathogenic bacterial strains, such as *S. aureus* MTCC-96 (Gram-positive) and *S. typhimurium* MTCC-98 (Gram-negative). The minimum inhibitory concentrations (*MIC*) were determined as per the recommendations of the Clinical and Laboratory Standards Institute (CLSI, www.clsi.org) on Muller–Hinton Agar containing serial twofold dilution of the drugs. MIC was taken after 48 h incubation along with positive and negative controls at 37 °C. Dimethyl sulphoxide was used as the solvent. Petri dishes with 100mm diameter were used.

For the antifungal activity, all the compounds were tested with a similar procedure as above against two different fungi: *A. niger* and *C. albicans*.

CONCLUSIONS

A series of novel substituted benzimidazole–quinoline derivatives was synthesized by condensation of *o*-phenylenediamine with [(5-chloroquinolin-8-yl)-oxy]acetic acid, followed by subsequent reactions of this compound with different electrophiles. All the compounds were subjected to biological screening and they showed promising antibacterial activity against *S. aureus* (Gram-positive) and *S. typhimurium* (Gram-negative), which were comparable to the activity of known standard drugs. This proves the high therapeutic value of these compounds and encourages further study to explore their biological potential. Some of the compounds (**4a, 4i, 4j** and **4l**) also exhibited good antifungal activity against *A. niger* but the antifungal activities against *C. albicans* were disappointing.

SUPPLEMENTARY MATERIAL

Analytical and spectral data of the synthesized compounds are available electronically at http://www.shd.org.rs/JSCS/, or from the corresponding author on request.

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ИЗВОД

СИНТЕЗА И АНТИБИКРОБНА АКТИВНОСТ НОВИХ *N*-СУПСТИТУИСАНИХ 8-(1-АЛКИЛ/АЛКИЛСУЛФОНИЛ/АЛКОКСИКАРБОНИЛ-БЕНЗИМИДАЗОЛ-2--ИЛМЕТОКСИ)-5-ХЛОРХИНОЛИНА

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У раду је приказана синтеза серије нових деривата 8-(1-алкил/алкилсулфонил/алкоксикарбонил-бензимидазол-2-илметокси)-5-хлорхинолина. Једињења су добијена кондензацијом *о*-фенилендиамина и [(5-хлорхинолин-8-ил)окси]сирћетне киселине, после чега је уследила супституција на азоту различитим електрофилним реагенсима у присуству одговарајуће базе чиме је добијена серија хетероцикличних једињења која садрже бензимидазолско и хинолинско језгро. Структуре једињења потврђене су спектралним подацима – ^{1}H-NMR, ^{13}C-NMR, ИС и масеним спектрима. Готово сва једињења показују значајну антибактеријску активност према *Salmonella typhimurium* и *Staphylococcus aureus*. Нека од њих показују добру антифунгалну активност према *Aspergillus niger*, али је антифунгална активност према *Candida albicans* веома слаба.

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REFERENCES

1. G. Coban, S. Zencir, I. Zupko, B. Rethy, H. S. Gunes, Z. Topcu, *Eur. J. Med. Chem.* **44** (2009) 2280
2. M. Amari, M. Fodili, B. Nedjar-Kolli, *J. Heterocycl. Chem.* **39** (2002) 811
3. A. Kozo, A. Kazuhiro, K. Masayuki, Y. Yongzhe (Fuji Photo Film Co. Ltd.), US 6815455 (2001)
4. J. A. Robl, R. Sulsky, C. Q. Sun, L. M. Simpkins, T. Wang, J. K. Dickson Jr., Y. Chen, D. R. Magnin, P. Taunk, W. A. Slusarchyk, S. A. Biller, S. J. Lan, F. Connolly, L. K. Kunselman, T. Sabrah, H. Jamil, D. Gordon, T. W. Harrity, J. R. Wetterau, *J. Med. Chem.* **44** (2001) 851
5. S. K. Katiyar, V. R. Gordon, G. L. McLaughlin, T. D. Edlind, *Antimicrob. Agents Chemother*. **38** (1994) 2086
6. H. D. Langtry, M. I. Wilde, *Drugs* **56** (1998) 447
7. K. Nagata, N. Sone, T. Tamura, *Antimicrob. Agents Chemother*. **45** (2001) 1522
8. P. C. Garcia, R. M. Rivero, L. R. Lopez-Lefebre, E. Sanchez, J. M. Ruiz, L. Romero, *J. Agric. Food Chem.* **49** (2001) 131
9. L. Crocetti, A. Maresca, C. Temperini, R. A. Hall, A. Scozzafava, F. A. Muhlschlegel, C. T. Supuran, *Bioorg. Med. Chem. Lett.* **19** (2009) 1371
10. F. Awouters, C. J. E. Niemegeers, J. V. Berk, J. M. V. Nueten, F. M. Lenaerts, M. Borgers, K. H. L. Schellekens, A. Broeckaert, J. D. Cree, P. A. J. Janssen, *Cell. Mol. Life Sci.* **33** (1977) 1657
11. P. R. Graves, J. J. Kwiek, P. Fadden, R. Ray, K. Hardeman, A. M. Coley, M. Foley, T. A. J. Haystead, *Mol. Pharmacol.* **62** (2002) 1364
12. L. W. Scheibel, A. Adler, *Mol. Pharmacol*. **20** (1981) 218
13. H. Andersag, S. Breitner, H. Jung (Winthrop Chem. Co. Inc.), US 2233970 (1941)
14. E. Senn (J. R. Geigy A. G.), US 2411670 (1946)
15. D. S. Goldfarb (University of Rochester), US 2009/0163545A1 (2009)
16. C. Bhat, *Indian J. Heterocycl. Chem.* **5** (1995) 111
17. Dynachim (Chimetron S. A. R. L.), FR 1504627 (1967)
18. Dynachim (Chimetron S. A. R. L.), BE 696711 (1967)
19. A. Hubele (Ciba-Geigy Corporation), US 4902340 (1990)
20. G. Hynd, J. G. Montana, H. Finch, S. Ahmed, M. Domostoj, J. Moise, R. Arienzo (Argenta Discovery Ltd.), WO 2009/060209A1 (2009)
21. D. S. Rane, P. D. Joshi, IN 1126/MUM/2006A
22. M. A. Phillips, *J. Chem. Soc.* (1928) 2393
23. W. C. Guida, D. J. Mathre, *J. Org. Chem.* **45** (1980) 3172
24. I. A. Potapova, *Pharm. Chem. J.* **35** (2001) 588
25. P. R. Kumar, *Indian J. Chem., B* **25** (1986) 1273
26. K. Nagata, T. Itoh, M. Okada, A. Ohsawa, *Tetrahedron* **52** (1996) 6569.