ARTICLE

Synthesis, Characterization and Bioactivity of Propranolol and its Compounds

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Asian Pub. Corp.

www.asianpubs.org

Asian Journal of Organic & Medicinal Chemistry

Volume: 8 Year: 2023
Issue: 3–4 Month: July–December
pp: 23–28
DOI: https://doi.org/10.14233/ajomc.2023.AJOMC-P26570

Received: 2 July 2023
Accepted: 20 December 2023
Published: 9 January 2024

ABSTRACT

The conventional method used for β-blocker synthesis was initiated by refluxing biphenyl-2-ol (**1**) with an epoxy ring (**2**) in the presence of K_2CO_3 to obtain 2-[(biphenyl-2-yloxy)methyl]oxirane (**3**). Compound **3** was then reacted with 99% isopropylamine (**4**) and various substituted phenols (**6a-i**) to obtain 1-(biphenyl-2-yloxy)-3-(propan-2-ylamino)-propan-2-ol (**5**) and 1-(2,6-dimethyl-/4-methoxy-/4-chloro-3-hydroxy-/2,6-dimethoxy-/3,4-dimethyl-/4-amine-/4-bromo/3,4-dinitro-/2,4-dihydroxyphenoxy)-3-(biphenyl-2-yloxy)propan-2-ols (**7a-i**), respectively. The purity of the synthesized compounds was confirmed by melting point and thin layer chromatography. The synthesized compounds were analyzed by ^{1}H NMR and FTIR spectroscopy to determine their structure. These compounds were also evaluated for their antifungal activity against *Rhizoctonia solani* and *Aspergillus niger* using the food poison technique. From the activity data, it was found that compound 1-(biphenyl-2-yloxy)-3-(propan-2-ylamino)propan-2-ol (**5**) was most active against both fungi *R. solani* and *A. niger*. Antibacterial activity was also determined against *Bacillus* species by zone of inhibition method. Compounds **5** and **7a-i** were also evaluated for its herbicide activity.

KEYWORDS

Propranolol, β-Blockers, Antifungal, Herbicidal activity, Antibacterial activity.

INTRODUCTION

Propranolol is widely used as an inhibitor in the field of medicine to treat angina, hypertension, glaucoma, pectoris-obesity and other cardiovascular diseases [1]. Oral propranolol is an effective, safe and fast acting drug for the treatment of childhood hemangiomas and can be monitored on an outpatient basis [2]. Heterocyclic compounds containing oxygen, nitrogen and sulfur are the building blocks used for the synthesis of various compounds with medicinal or biological properties. In this work, a novel multisteps methodology for the synthesis of propranolol and its related compounds research was employed. In this first, we reflux biphenyl-2-ol with epichlorhydrin then the formed compound was further treated with isopropylamine to yield propranolol (**5**). Compound **3** was also treated with substituted phenols to give compounds **7a-i**. These compounds are important constituents of dyes, copolymers, antioxidants, *etc*.

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EXPERIMENTAL

The melting point was checked on board the electrical equipment for the Gensen melting point and are uncorrected. The homogeneity of the compounds was monitored regularly on silica gel G TLC plates using ethyl acetate:hexane (3:7) as the eluent. FTIR spectra were recorded on the Perkin-Elmer FTIR spectrophotometer using KBr method. ^{1}H NMR spectra were recorded on a Bruker Avance II 400F (400 MHz) NMR spectrophotometer in $CDCl_3$ or DMSO-d_6 solvent using TMS as an internal reference.

Synthesis of 1-(biphenyl-2-yloxy)-3-(propan-2-yl-amino)-propan-2-ol (5) and 1-(2,6-dimethyl-/4-methoxy-/4-chloro-3-hydroxy-/2,6-dimethoxy-/3,4-dimethyl-/4-amine-/4-bromo-/3,4-dinitro-/2,4-dihydroxyphenoxy)-3-(biphenyl-2-yloxy)propan-2-ols (7a-i): Biphenyl-2-ol (**1**) was refluxed on oil bath with epichlorohydrin (**2**) in the presence of anhydrous K_2CO_3 to obtain 2-[(biphenyl-2-yloxy)methyl]oxirane (**3**). The compound (**3**) was then reacted with 99% isopropylamine (**4**) and various substituted phenols (**6a-i**) to form 1-(biphenyl-2-yloxy)-3-(propan-2-ylamino)propan-2-ol (**5**) and 1-(2,6-dimethyl-/4-methoxy-/4-chloro-3-hydroxy-/2,6-dimethoxy-/3,4-dimethyl-/4-amine-/4-bromo-/3,4-dinitro-/2,4-dihydroxyphenoxy)-3-(biphenyl-2-yloxy)propan-2-ols (**7a-i**), respectively (**Scheme-I**).

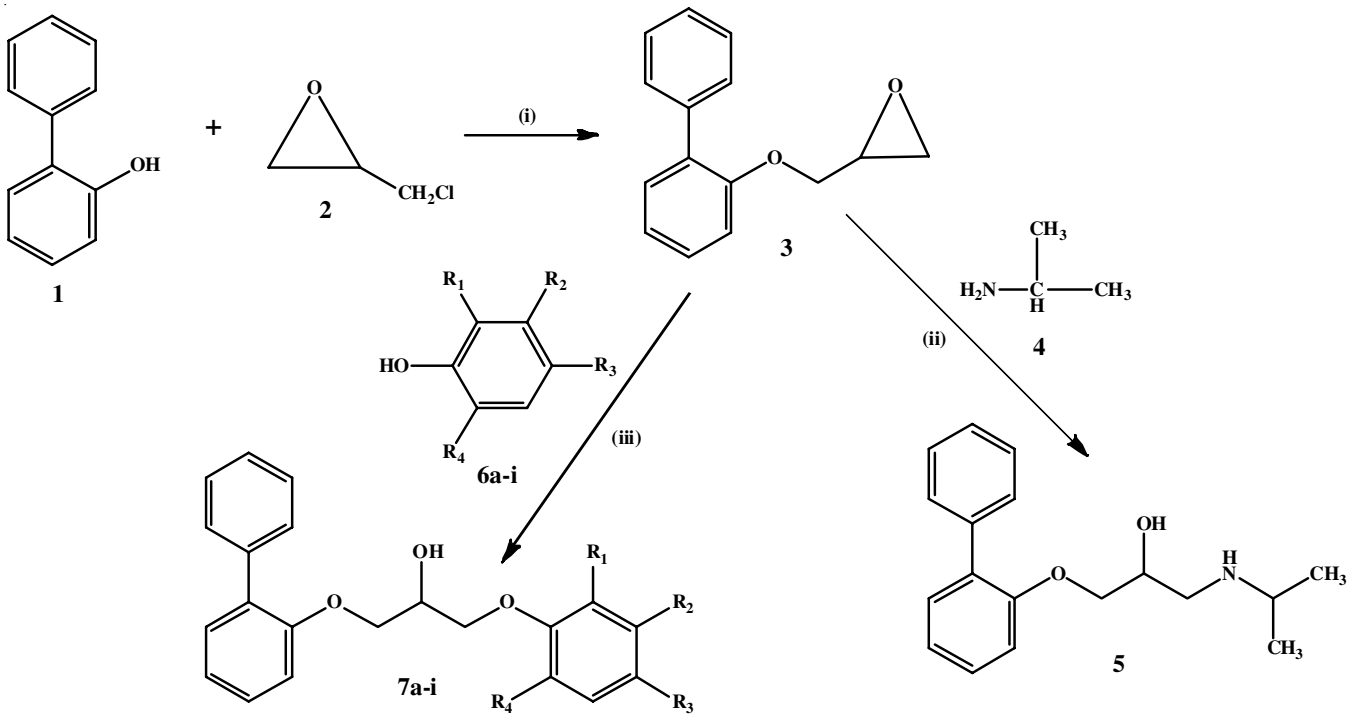
2-[(Biphenyl-2-yloxy)methyl]oxirane (3): Yield 85%, viscous mass, m.f. $C_{15}H_{13}O_2$, IR (KBr, ν_{max}, cm^{-1}): 1400 (C-CH_3), 1550 (C=C, aromatic), 3410 (NH), 3520 (OH). Elemental analysis of $C_{15}H_{13}O_2$ calcd. (found) %: C, 80.07 (80.05); H, 5.74 (5.72).

1-(Biphenyl-2-yloxy)-3-(propan-2-ylamino)propan-2-ol (5): Yield 71%, m.p.: 93-95 °C, m.f. $C_{18}H_{23}NO_2$, IR (KBr, ν_{max}, cm^{-1}): 1112 (C-O-C), 1446 (C-CH_3), 1592 (C=C, aromatic), 3362 (NH), 3482 (OH); ^{1}H NMR ($CDCl_3$) δ ppm: 2.59 (s, 3H, CH_3), 3.24 (m, 1H, CH). Elemental analysis of $C_{18}H_{23}O_2N$ calcd. (found) %: C, 75.83 (75.79); H, 8.10 (8.07); N, 5.66 (4.91).

1-(2,6-Dimethylphenoxy)-3-(biphenyl-2-yloxy)propan-2-ol (7a): Yield 78%, viscous mass, m.f. $C_{23}H_{24}O_3$, IR (KBr, ν_{max}, cm^{-1}): 1105 (C-O-C), 1400 (C-CH_3), 1550.0 (C=C, aromatic), 3530 (OH); ^{1}H NMR ($CDCl_3$) δ ppm: 3.12 (s, 6H, 2CH_3), 3.42 (m, 1H, CH), 7.35 (dd, Ar-H). Elemental analysis of $C_{23}H_{24}O_3$ calcd. (found) %: C, 79.34 (79.31); H, 6.92 (6.89).

1-(4-Methoxyphenoxy)-3-(biphenyl-2-yloxy)propan-2-ol (7b): Yield 76%, viscous mass, m.f. $C_{22}H_{22}O_4$, IR (KBr, ν_{max}, cm^{-1}): 1106 (C-O-C), 1220 (OCH_3), 1550 (C=C, aromatic), 3547 (OH); ^{1}H NMR ($CDCl_3$) δ ppm: 3.45 (s, 3H, OCH_3), 3.49 (m, 1H, CH), 6.2-7.89 (m, 5H, Ar-H). Elemental analysis of $C_{22}H_{22}O_4$ calcd. (found) %: C, 75.46 (75.43); H, 6.29 (6.28).

1-(4-Chloro-3-hydroxyphenoxy)-3-(biphenyl-2-yloxy)-propan-2-ol (7c): Yield 78%, viscous mass, m.f. $C_{21}H_{19}O_4Cl$, IR (KBr, ν_{max}, cm^{-1}): 817 (C-Cl), 1092 (C-O-C), 1550 (C=C aromatic), 3553 (OH); ^{1}H NMR ($CDCl_3$) δ ppm: 3.50 (m, 1H, CH), 6.35-7.89 (m, 5H, Ar-H). Elemental analysis of $C_{21}H_{19}O_4Cl$ calcd. (found) %: C, 68.15 (68.11); H, 5.17 (5.14).



Compound No.	R_1	R_2	R_3	R_4	Compound No.	R_1	R_2	R_3	R_4
6a, 7a	CH_3	H	H	CH_3	**6f, 7f**	H	H	NH_2	H
6b, 7b	H	H	OCH_3	H	**6g, 7g**	H	H	Br	H
6c, 7c	H	OH	Cl	H	**6h, 7h**	H	NO_2	NO_2	H
6d, 7d	OCH_3	H	H	OCH_3	**6i, 7i**	OH	H	OH	H
6e, 7e	H	CH_3	CH_3	H					

Scheme-I: Reagents and reaction conditions: (i) anhydrous K_2CO_3, reflux; (ii) methanol, reflux; (iii) ethanol, NaOH, reflux

1-(2,6-Dimethoxyphenoxy)-3-(biphenyl-2-yloxy)-propan-2-ol (7d): Yield 74%, viscous mass, m.f. $C_{23}H_{24}O_5$, IR (KBr, ν_{max}, cm^{-1}): 1112 (C-O-C), 1220 (OCH_3), 1550 (C=C, aromatic), 3550 (OH); ^1H NMR ($CDCl_3$) δ ppm: 3.45 (s, 6H, OCH_3), 3.59 (m, 1H, CH), 6.35-7.91 (m, 5H, Ar-H). Elemental analysis of $C_{23}H_{24}O_5$ calcd. (found) %: C, 72.65 (72.63), H, 6.33 (6.32).

1-(3,4-Dimethylphenoxy)-3-(biphenyl-2-yloxy)propan-2-ol (7e): Yield 82%, viscous mass, m.f. $C_{23}H_{24}O_3$, IR (KBr, ν_{max}, cm^{-1}): 1110 (C-O-C), 1400 (C-CH_3), 1550 (C=C, aromatic), 3540 (OH); ^1H NMR ($CDCl_3$): 2.71 (s, 6H, CH_3), 3.42 (m, 1H, CH), 6.12-7.51 (m, 5H, Ar-H). Elemental analysis of $C_{23}H_{24}O_3$ calcd. (found) %: C, 79.33 (79.31); H, 6.92 (6.90).

1-(4-Aminephenoxy)-3-(biphenyl-2-yloxy)propan-2-ol (7f): Yield 78%, viscous mass, m.f. $C_{21}H_{21}NO_3$, IR (KBr, ν_{max}, cm^{-1}): 1112 (C-O-C), 1550 (C=C, aromatic), 3420 (NH), 3540 (OH); ^1H NMR ($CDCl_3$) δ ppm: 3.84 (m, 1H, CH), 5.03 (s, 2H, NH), 6.42-7.69 (m, 5H, Ar-H). Elemental analysis of $C_{21}H_{21}O_3N$ calcd. (found) %: C, 75.24 (75.22); H, 6.28 (6.27); N, 4.21 (4.18).

1-(4-Bromophenoxy)-3-(biphenyl-2-yloxy)propan-2-ol (7g): Yield 70%, viscous mass, m.f. $C_{21}H_{19}O_3Br$, IR (KBr, ν_{max}, cm^{-1}): 650 (C Br), 1110 (C-O-C), 1598 (C=C, aromatic), 3550 (OH); ^1H NMR ($CDCl_3$) δ ppm: 3.94 (m, 1H, CH), 6.51-7.89 (m, 5H, Ar -H). Elemental analysis of $C_{21}H_{19}O_3Br$ calcd. (found) %: C, 63.19 (63.16); H, 4.79 (4.76).

1-(3,4-Dinitrophenoxy)-3-(biphenyl-2-yloxy)propan-2-ol (7h): Yield 79%, viscous mass, m.f. $C_{21}H_{20}N_2O_7$, IR (KBr, ν_{max}, cm^{-1}): 1115 (C-O-C), 1570 (NO_2), 1598 (C=C, aromatic), 3520 (OH); ^1H NMR ($CDCl_3$) δ ppm: 4.32 (m, 1H, CH), 6.87-8.00 (m, 5H, Ar-H). Elemental analysis of $C_{21}H_{20}O_7N_2$ calcd. (found) %: C, 61.20 (61.17); H, 4.87 (4.85); N, 6.83 (6.80).

1-(2,4-Dihydroxyphenoxy)-3-(biphenyl-2-yloxy)-propan-2-ol (7i): Yield 81%, viscous mass, m.f. $C_{21}H_{20}O_4$, IR (KBr, ν_{max}, cm^{-1}): 1118 (C-O-C), 1597 (C=C, aromatic), 3540 (OH); ^1H NMR ($CDCl_3$) δ ppm: 2.91 (m, 1H, CH), 4.15 (broad, 2H, OH), 6.13-7.21 (m, 5H, Ar-H). Elemental analysis of $C_{21}H_{20}O_4$ calcd. (found) %: C, 75.59 (75.57); H, 5.98 (5.95).

Herbicidal activity: A solution of 50 µg/mL, 100 µg/mL and 150 µg/mL of the test compound in DMSO solvent was prepared. The agar powder (5 g) was put in boiling distilled water (1 L) until it dissolved and then cooled to 40-50 ºC. The solution (2 mL) containing the test compounds and the melting agar (18 mL) was mixed and this mixture was added to a 4.5 cm diameter petri dish. The agar plate without test compound was used as an untreated control. The seeds of *Raphanus sativus* L. (radish) were deposited on the surface of the agar plate. The petridish were covered with glass lids and the culture conditions were maintained alternately for 7 days at 25 ± 1 ºC and 12 h in light and 12 h in dark. Seven days later, the root and shoot lengths of *Raphanus sativus* L. were measured. The rate of growth inhibition bound to the untreated control was determined by a given formula:

$$\text{Inhibition } (\%) = \frac{C - T}{C} \times 100$$

C = mycelia development in control dish; T = mycelia development in treated dish.

Antibacterial activity: The *Bacillus* strain was grown in the lab on Luria-Bertani medium. Antibacterial activity was tested using the zone inhibition method. Concentrations of 50, 100, 150 and 200 µg/mL synthesized compounds were prepared from the stock solution by taking the appropriate amount and diluting with DMSO solvent. DMSO was used as a negative control. The 10 mm diameter circular paper discs were made from Whatman's No. 1 filter paper. The discs were placed in a Petri plate and autoclaved at 15 lbs pressure for 20 min. Two paper discs were used for each concentration of the synthesized compounds. The excess solution absorbed by the paper discs was removed by holding them vertically with sterile forceps. These soaked discs were aseptically transferred to Petri plates containing media and a bacterial suspension was smeared on the surface. The Petri plates were kept overnight in an incubator at 25 ± 2 °C and then examined for the zone of inhibition at these different concentrations of compounds. The experiment was performed in triplicate and the activity was determined based on the zone of inhibition (mm).

Antifungal activity: The synthesized compounds (**5**, **7a-i**) were evaluated for their antifungal activity against *Rhizoctonia solani* and *Aspergillus niger*, respectively. The fungal species were grown in the laboratory on potato dextrose agar (PDA) media. The antifungal activity was determined by the food poisoning technique method. The required amount of synthetic compound dissolved in 1 mL of DMSO was aseptically introduced into a 99 mL aliquot of sterile potato dextrose agar, which was cooled to 45 ºC after brief stirring. Each batch of media was poured into Petri dishes and allowed to solidify. DMSO was used as a negative control. Each plate was inoculated centrally with 5 mm pieces of mycelium from the periphery of the 2-3 day old fungal colony. The inoculated Petri dishes were incubated in the dark at 25 ± 2 ºC for 48-72 h and the colony diameter was measured periodically until the control plates were almost completely covered by fungal growth. All the experiments were made in triplicate. The degree of growth inhibition was calculated from the mean differences between the treatments and the control as a percentage of latter using formula:

$$\text{Inhibition } (\%) = \frac{C - T}{C} \times 100$$

C = mycelia growth in control dish, T = mycelia growth in treated dish.

RESULTS AND DISCUSSION

Condensation of biphenyl-2-ol (**1**) with epichlorohydrin (**2**) in the presence of anhydrous K_2CO_3 was refluxed on oil bath. The excess epichlorohydrin was evaporated to obtain 2-[(biphenyl-2-yloxy)methyl]oxirane (**3**) by conventional method. The progress of the reaction was monitored by TLC technique. Compound (**3**) was further reacted with 99% isopropylamine (**4**) and refluxed on water bath. The excess of isopropylamine was evaporated to dryness in vacuum. The remainder was extracted between 2 N HCl and ether. The HCl layer was neutrallized with 1 N NaOH. The formed product (**5**) was filtered and recrystallized from ethyl acetate to afford a crystalline solid in 71% yield. The ^1H NMR spectrum of compound **5** in $CDCl_3$ displayed a doublet at δ 2.59 integrating for three protons for methyl functionality. A characteristic multiplet appeared at δ 3.24 for

one proton of CH. The compound showed IR absorption peak at 3482, 3362 and 1592 cm^{-1} indicated the presence of OH, NH and C=C aromatic, respectively. Based on the above data the compound was assigned the structure as 1-(biphenyl-2-yloxy)-3-(propan-2-ylamino)propan-2-ol.

Compound **3** was then reacted with 2,6-dimethyl phenol **(6a)**, 4-methoxy phenol **(6b)**, 4-chloro-2-hydroxy phenol **(6c)**, 2,6-dimethoxy phenol **(6d)**, 3,4-dimethyl phenol **(6e)**, 4-amine phenol **(6f)**, 4-bromo phenol **(6g)**, 3,4-dinitro phenol **(6h)** and 2,4-dihydroxy phenol **(6i)** in presence of ethanol and NaOH as a catalyst refluxed on water bath for 8 h (**Scheme-I**). The ^1H NMR spectrum of compound **7a** in $CDCl_3$ solvent displayed a singlet at δ 3.12 integrating for six protons for methyl functionality. A characteristic multiplet appeared at δ 3.42 for one proton of CH. The compound showed IR absorptions at 3530, 1400 and 1550 cm^{-1} indicated the presence of OH, C-CH_3 and C=C aromatic, respectively. Based on the above data, compound was assigned the structure as 2,6-dimethylphenoxy)-3-(biphenyl-2-yloxy)propan-2-ol (**7a**). The other compounds **7b-i** were also synthesized by similar method.

Antifungal activity: All the synthesized compounds **(5** and **7a-i)** were evaluated for their antifungal activity against two fungal strains *viz. Rhizoctonia solani* and *Aspergillus niger* by the method of food poisoned technique method. The results of antifungal activity of tested compounds is shown in Table-1 and Fig. 1. It was found that compound **5** was the most active against both the tested fungi *Rhizoctonia solani* and *Aspergillus niger* with EC_{50} value 48.00 and 52.91 µg/mL. All other compounds showed the least toxicity against both the tested fungi.

Antibacterial activity: All the synthesized compounds (**5** and **7a-i**) were screened for their *in vitro* antibacterial activity against *Bacillus* species by the zone of inhibition method using DMSO as a negative control. The results of the antibacterial activity of the synthesized compounds are shown in Table-2 and Fig. 2. Compound **7c** showed the highest toxicity, further it was observed that chlorine and methyl substituents at different positions in a series of compounds showed the highest activity.

Herbicidal activity: All compounds (**5** and **7a-i**) were screened for herbicidal activity against *Raphanus sativus* L. at various concentrations *viz.* 200, 150, 100 and 50 µg/mL is shown in Table-3. Herbicidal activities of the compounds were evaluated against *Raphanus sativus* L. by inhibitory effect of compounds on the growth of weed roots and shoots. Compound **7d** showed the highest growth inhibition in both roots and shoots of *Raphanus sativus L.* at all the tested concentrations (Fig. 3). Whereas compound **7h** showed the minimum toxicity in this series. The growth inhibition may be attributed to substitution of methoxy and nitro groups on the phenyl ring.

TABLE-1
FUNGI TOXICITY OF 1-(BIPHENYL-2-YLOXY)-3-(PROPAN-2-YLAMINO)PROPAN-2-OL (**5**) AND 1-(2,6-DIMETHYL-/4-METHOXY-/4-CHLORO-3-HYDROXY-/2,6-DIMETHOXY-/3,4-DIMETHYL-/4-AMINE-/4-BROMO-/3,4-DINITRO-/2,4-DIHYDROXYPHENOXY)-3-(BIPHENYL-2-YLOXY)PROPAN-2-OLS (**7a-i**)

Compd. No.	Growth inhibition (%)								*Rhizoctonia solani*	*Aspergillus niger*
	Rhizoctonia solani				*Aspergillus niger*					
	50 µg/mL	100 µg/mL	150 µg/mL	200 µg/mL	50 µg/mL	100 µg/mL	150 µg/mL	200 µg/mL	EC_{50} (µg/mL)	EC_{50} (µg/mL)
5	38.57	47.14	54.28	62.85	48.62	72.35	75.32	79.63	48.00	52.91
7a	35.68	49.37	59.48	69.32	43.64	50.37	58.23	69.72	103.12	97.65
7b	44.28	52.83	61.15	67.37	33.49	46.56	57.39	66.32	83.45	115.88
7c	44.28	49.05	59.54	67.32	37.32	45.58	57.47	66.42	104.53	118.59
7d	–	–	–	–	33.45	37.52	45.24	54.87	–	174.72
7e	47.14	57.14	67.15	72.14	35.68	49.37	59.48	69.32	64.30	103.12
7f	32.85	45.71	56.77	66.25	–	–	–	–	119.39	–
7g	32.85	48.57	60.00	70.00	32.47	40.32	49.73	60.03	106.34	151.31
7h	–	–	–	–	–	–	–	–	–	–
7i	39.97	48.23	55.78	63.54	33.56	43.00	57.65	68.32	111.72	123.90

– = No growth inhibition

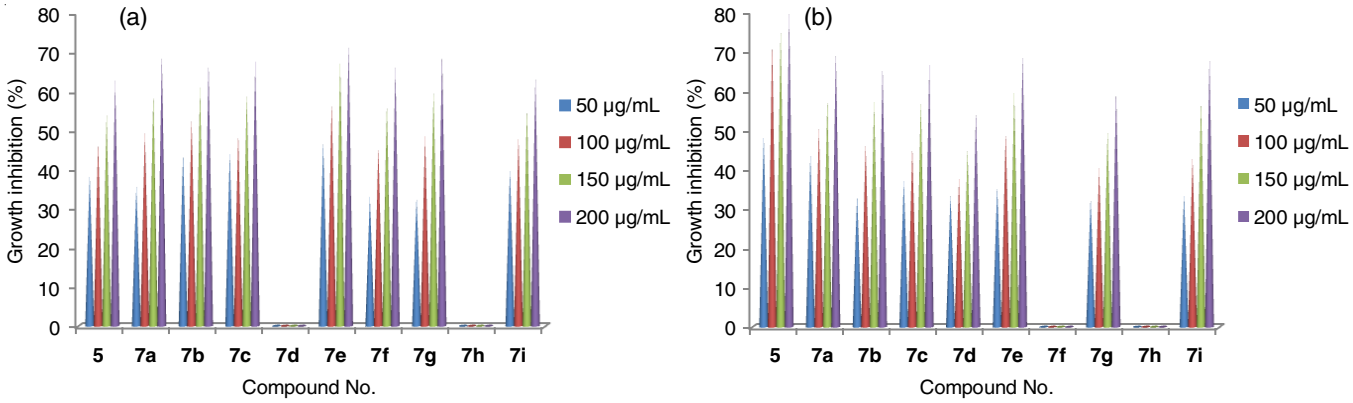


Fig. 1. Fungi toxicity of substituted propranolols (**5**, **7a-i**) against (a) *Rhizoctonia solani* and (b) *Aspergillus niger*

TABLE-2
ANTIBACTERIAL ACTIVITY OF 1-(BIPHENYL-2-YLOXY)-3-(PROPAN-2-YLAMINO)PROPAN-2-OL (5) AND 1-(2,6-DIMETHYL-/4-METHOXY-/4-CHLORO-3-HYDROXY-/2,6-DIMETHOXY-/3,4-DIMETHYL-/4-AMINE-/4-BROMO-/3,4-DINITRO-/2,4-DIHYDROXYPHENOXY)-3-(BIPHENYL-2-YLOXY)PROPAN-2-OLS (**7a-i**)

Compd. No.	*Bacillus* species: Zone inhibition (mm)			
	50 µg/mL	100 µg/mL	150 µg/mL	200 µg/mL
5	–	–	8.50	15.00
7a	13.00	29.50	36.00	45.50
7b	–	–	–	–
7c	3.50	8.00	13.50	20.00
7d	–	–	9.00	16.00
7e	11.50	26.00	35.50	49.00
7f	–	–	–	–
7g	–	–	12.00	43.00
7h	4.00	7.50	10.00	15.50
7i	–	–	–	–

– = No growth inhibition

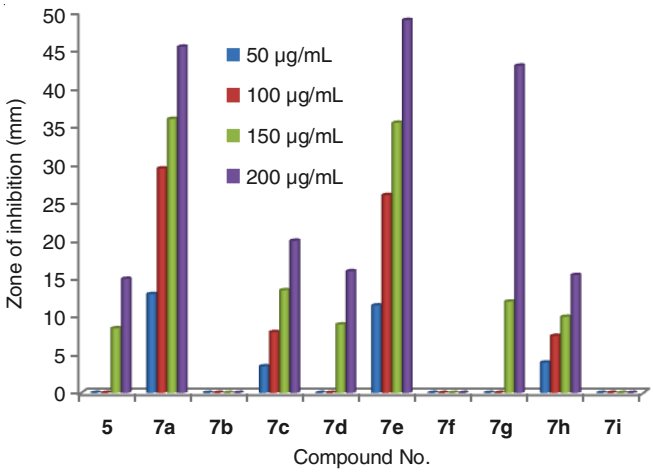


Fig. 2. Antibacterial activity of substitutd propranolols (**5**, **7a-i**) against *Bacillus* species

Conclusion

An alternative multistep reaction for the synthesis of propranolol and its compounds has been developed compared to the previous report. This route is simple, inexpensive and can be taken in conditions that are not too tideous. The bio-efficacy of synthesized compounds (**5 and 7a-i**) in relation to herbicidal activity against *Raphanus sativus* L. (radish) seeds, antibacterial activity against *Bacillus* species and antifungal activity against *Rhizoctonia solani* and *Aspergillus niger* were successfully evaluated.

ACKNOWLEDGEMENTS

The authors are thankful to the Department of Chemistry, Chaudhary Charan Singh Haryana Agricultural University, Hisar for providing the necessary facilities. The authors are also thankful to SAIF, Punjab University Chandigarh, India for providing the analytical facilities for characterization of compounds.

TABLE-3
HERBICIDAL ACTIVITY OF 1-(BIPHENYL-2-YLOXY)-3-(PROPAN-2-YLAMINO)PROPAN-2-OL (**5**) AND 1-(2,6-DIMETHYL-/4-METHOXY-/4-CHLORO-3-HYDROXY-/2,6-DIMETHOXY-/3,4-DIMETHYL-/4-AMINO-/4-BROMO-/3,4-DINITRO-/2,4-DIHYDROXYPHENOXY)-3-(BIPHENYL-2-YLOXY)PROPAN-2-OLS (**7a-i**)

Compd. No.	Inhibition (%)							
	Root				Shoot			
	50 µg/mL	100 µg/mL	150 µg/mL	200 µg/mL	50 µg/mL	100 µg/mL	150 µg/mL	200 µg/mL
5	50.06	57.70	69.54	75.00	50.00	56.45	66.05	73.30
7a	54.78	60.00	70.56	77.54	54.98	57.73	68.90	74.37
7b	58.63	65.74	74.00	80.53	56.05	62.06	73.26	76.59
7c	63.89	69.07	76.48	88.00	61.93	65.07	74.57	84.58
7d	68.90	75.96	80.72	90.45	64.17	73.00	77.46	87.56
7e	64.06	71.54	78.46	89.54	62.00	67.43	75.00	83.41
7f	61.13	68.79	76.13	84.05	58.04	64.60	71.04	78.74
7g	59.63	66.03	79.02	87.90	54.31	61.00	63.30	81.03
7h	53.07	58.80	65.90	71.03	52.87	54.06	63.32	67.46
7i	63.75	69.48	74.35	80.00	61.05	65.50	73.78	78.56

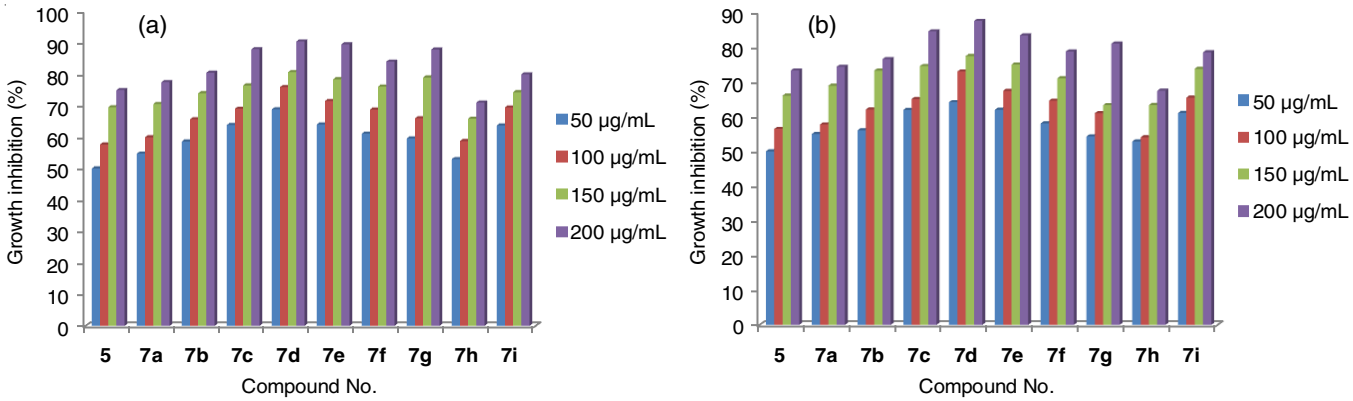


Fig. 3. Herbicidal activity of substituted propranolols (**5**, **7a-i**) in (a) root and shoot

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